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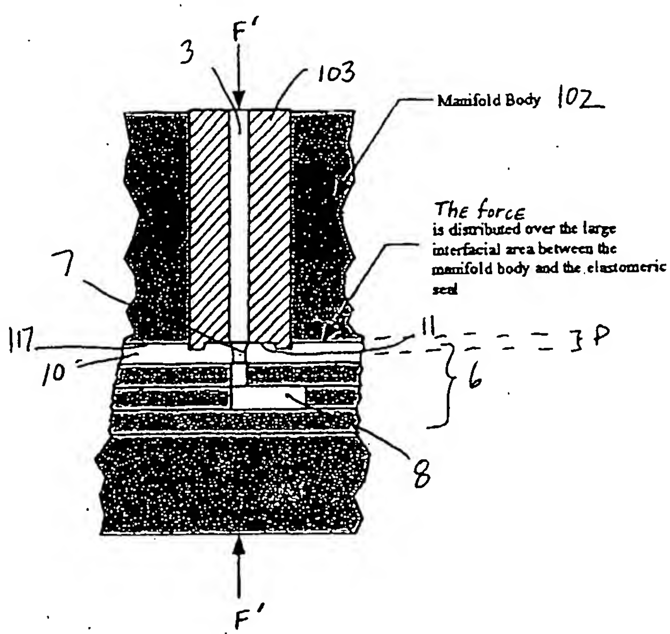

(57) Abstract: Interconnect configurations and an interconnect manifold for microfluidic devices (6) is provided. Devices for introducing one or more gases or removing gases from microfluidic cavity elements (8) is also provided. The invention is also directed to methods for making interconnects and to methods for delivery or removal of gasses from microfluidic devices (6).

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FLUIDIC INTERCONNECT, INTERCONNECT MANIFOLD AND MICROFLUIDIC DEVICES FOR INTERNAL DELIVERY OF GASES AND APPLICATION OF VACUUM

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CROSS-REFERENCE TO RELATED APPLICATIONS

This application takes priority under 35 U.S.C. 119(e) to U.S. provisional application 60/146,023 filed July 28, 1999.

BACKGROUND OF THE INVENTION

The present invention relates generally to microfluidic devices and particularly to means and methods for delivery or removal of fluids, including provision of vacuum, to microchannels and device elements in a microfluidic device. More specifically, the invention relates to fluid interconnects between a meso- or macroscaled environment to a microscaled environment. The invention also relates to means and methods for application of a vacuum to microfluidic channels in a microfluidic device to facilitate degassing of the channel and device. Specific applications of the internal degassing system are provided.

With the advent of micromachining technology, microfluidic devices have proliferated and are now widely applied in environmental and biological analyses. A practical limitation of efficient, reliable and economic use of such devices is the interface between the microscale environment of the device and meso- and macroscale environments to be sampled or to which samples are passed for analyses. The interface is accomplished by interconnects which require the use of some type of seal. These interfaces can often be the weak link in a

microfluidic system and because such small volumes are typically being processed, the smallest of leaks, or unplanned entrapments of air, can cause a microfluidic system to fail.

Prior art methods for making interconnects to microfluidic devices include the use of glass tubes sealed with epoxy. Additionally, it is known to employ septa which are pierced by needles or tubes to make an interconnect. U.S. patent 6,090,251 of Sundberg et al. reports the use of a port in fluid communication with a microfluidic channel. A pipette or other device is used to deliver fluid to the port.

This invention provides a fluid interconnect design which is readily implemented in microfluidic devices, particular in multiple layer laminate microfluidic devices, and which provides stronger, and more durable that are less susceptible to geometric irregularities. The invention also provides a fluid interconnect manifold which is readily adaptable to a number of interconnect configurations and provides for establishing a plurality of interconnects in a simple clamping operation.

A common misconception in fluid interconnect design is that increased seal interface area always leads to an improved. There are some sealing applications where this is true, but in general it is not important how much seal area there is, but rather that the interfacial stress in the seal regions is sufficient to ensure a robust fluid interconnect. If the fluid pressure exceeds the interfacial stresses, the interconnect fails (e.g. leaks). This principle applies to the simplest of seals, the face seal between the flat face of a rigid tube and an elastomer seal. Face seal are of particular interest for forming interconnects with microfluidic devices because elastomer sealing layers with microvia for connection to microchannels can be readily implemented in such devices. However, face seals are very sensitive to minor angular or linear misalignments or any geometric irregularities of the tube or elastomer. Any tubing flexibility will allow the tube end face to slip or wander on the elastomer and out of alignment with the microvia. Further, in a simple flat face seal, the sealing action is distributed over the maximum seal area (the area of contract of the tubing end face with the elastomer. This generally requires that more force be applied to insure adequate interfacial seal stress at all locations around the seal, Increased interfacial stress over portions of the seal leads to an

increased barreling of the seal elastomer material, leading to microvia closure and interconnect failure.

Supplying gases to and removing gases from liquids in a microfluidic device can be challenging, but represents an enabling method for performing a series of unique chemical and biological operations and microfluidic device and microsystem operations.

Device wet out can be a significant practical problem with microfluidic devices and can be a particularly difficult problem in broad, flat microfluidic channel or chambers (e.g., those in which the aspect ratio, i.e., channel width/depth) is greater than or equal to about 25 and is typically much greater). Numerous instances exit where it is also advantageous to have highly localized control of gas injection or removal of gases. Some instances are coupled to electrochemical electrolysis products, others will make interactions with magnetically based microbead reactions advantageous. Wet out of a microfluidic channel can be facilitated by degassing of the channel.

A variety of liquid degassing devices and methods which employ gas-permeable tubes, containers and membranes have been reported. See for example, U.S. patent 4,729,773; U.S. 4,516,984; 5,053,060 and 5,695,545. U.S. patent 5,053,060 reports a degasser which is used to remove gas bubbles or dissolved gases from a liquid stream. The degasser is formed from a hydrophobic membrane and two blocks: one having a grooved channel with an inlet and an outlet and the other with venting holes. The membrane is clamped between the two blocks over the channel. As liquid flows through the channel gas bubbles or dissolves gases pass through the membrane and are vented. The channel in the illustrated device is 0.2 mm deep, 1.5 mm wide and 120 mm long. The thin layer is said to facilitate rapid degassing. Degassing is reported to be facilitated by heat or vacuum.

The present invention provides means and methods for selectively applying a vacuum to one or more microfluidic cavity elements in a microfluidic device. An internal degassing system for a microfluidic device is provided. The system provides for rapid degassing to facilitate device wet out and/or to remove gas bubbles or dissolved gases that can disrupt

function of the device. The internal degassing system is particularly useful in combination with microfluidic devices that have wide, flat channels with width/depth aspect ratios greater than or equal to about 25 or devices in which vacuum must be supplied to different microfluidic cavity elements in the device.

A variety of methods are known in the art for introducing gases into liquid streams. Such methods are of particular interest for introducing oxygen into bioreactors or for oxygenating biological fluids, such as blood. One particularly challenging application in the microsystems field is the maintenance of an environment for the growth and study of single cells for proteomics analysis or functional genomics research where responses to environmental perturbations provide key information. Gas introduction is also of interest in chemical or enzymatic reactors in which a gas, such as oxygen is a substrate. Chemical and enzymatic reactions involving gaseous substrates can be employed in various analytical procedures. In addition, an undesired gas the is dissolved in a liquid can be replaced by introduction of another more desirable gas into the liquid. For example, dissolved oxygen which may react with a component in the liquid can be displaced from the liquid by bubbling a less reactive or non-reactive gas (e.g., nitrogen or an inert gas) through the liquid. The degasser device of U.S. patent 5,053,060 is also reported to function as a "Gasser" for introducing gases into liquids flowing though the channel formed between the blocks.

The present invention therefore also provides means and methods for selectively introducing one or more gases to one or more microfluidic cavity elements in a microfluidic device. An internal "gassing" system for a microfluidic device is provided. The system provides for rapid introduction of one or more gases with capability for control of the rate and partial pressure of gases introduced. The gassing system can also be used to displaced undesired dissolved gases with desired gases without disrupting the function of the device. The internal gas introduction system is particularly useful in combination with microfluidic devices that have wide, flat channels with width/depth aspect ratios greater than or equal to about 25 or devices in which one or more gases must be supplied to different microfluidic cavity elements in the device.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides interconnect configurations and interconnect manifold devices that provide reliable, robust seals to microfluidic channels in microfluidic devices. The interconnects can provide for fluidic connection for fluid delivery or removal from a microfluidic device.

More particularly, the invention provides a fluid interconnect between a macro- or mesofluidic channel and a microfluidic channel in a microfluidic device which forms a face seal. The interconnect comprises a rigid tube with a selected sized bore and having a sealing end face with one or more ridges around the perimeter of the tubing bore and an elastomer seal layer. The ridge is of a selected height and shape. The ridge can be positioned at any place on the end face, however in preferred embodiments the ridge is positioned at the perimeter of the tube or centrally between the tube perimeter and the bore perimeter. The elastomer layer is preferably planar and flat and has an upper sealing face. In a fluid interconnect the sealing end face of the rigid tube is positioned and held in contact with the upper sealing face of the elastomer seal layer such that the bore of the tube is aligned with a microvia of the elastomer seal layer and such that the force applied is sufficient to form a complete seal around the perimeter of the tubing bore. Force is typically applied to achieve a seal that withstands (i.e., does not leak) on application of a selected pressure. In a preferred embodiment, the force applied maximizes the seal engagement depth of the ridge in the elastomer.

The sealing end face of the tube can have one or more ridges having the same or different heights above the plane of the tubing bore. The ridge may have a variety of shapes including those with a flat (square) ridge, a pointed ridge (V-ridge) or a rounded ridge (e.g., semi-circle wave ridge).

In another embodiment, the invention provides a fluidic interconnect manifold for establishing one or more fluid connections between one or more macro- or mesofluidic channels and one or more microfluidic systems having one or more microfluidic devices and said devices being internally connected by microchannels. The microfluidic system (or

module) has at least one planar elastomer layer having one or more microvias extending through the elastomer layer. The microvias are each of in fluid communication with a microfluidic channel within the microfluidic system. The manifold comprises a manifold body having a top and bottom surface and a plurality of tube cavities extending through the body from the top to bottom surface of the manifold for receiving an interconnect tube and a plurality of rigid interconnect tubes each having a microchannel dimension bores and a sealing end face at one end of the tube. The other end of the tube is connected to a mesoscaled fluid supply or a vacuum supply for fluid removal. The sealing end face of the tube optionally has a ridge as described above to facilitate seal formation. Each tube extends below the bottom surface of the manifold body a selected distance. The distance is selected to obtain a desired seal engagement depth with the elastomer. Typically, the tube end will extend outward (protrude) from the bottom surface of the manifold the height of the ridge. In this case, the plane of the tubing bore is approximately level with the bottom surface of the manifold body. The tube is selective positioned in the tube cavity with the desired protrusion and locked into place in the cavity. The tube can be selective locked into the cavity employing a variety of mechanical devices or may simply be bonded into the cavity with an appropriate glue or epoxy. A selectively adjustable claim is cooperative attached to the manifold body to receive a microfluidic device so that the planar elastomer layer of the microfluidic device is positioned with respect to the interconnect tubes extending from the manifold body. The microfluidic device is also aligned with respect to the interconnect tubes so that one or more microvias in the elastomer layer are each aligned with the bore of an extending interconnect tube. The clamp allows the force of a face seal formed between the sealing end face of the tube and the elastomer layer to be adjusted. Various mechanical, electromechanical and pneumatic devices can be used to activate the clamp of the manifold.

The interconnect manifold of this invention provides a rapid, reproducible means for establishing fluid interconnects to a microfluidic device. The interconnect manifold of this invention may also be used to introduce electrical contacts that connect external electrical systems (e.g., power and voltage supplies, etc.) to internal microsystem electrical systems that are used for either device operation diagnostics, interconnect to internal electrical sensors, etc. In other contexts, the standard interconnect system may be configured to couple

fiber optics with microsystem optical waveguides (fiber optic or otherwise). Magnetic microcoil probes may also be located employing the manifold in certain configurations.

In another aspect, the present invention provides devices and methods for delivery of a gas or application of a vacuum to any microfluidic channel, reservoir, chamber or device element in a microfluidic device. Gas can be delivered to and vacuum can be applied continuously or selectively as desired and can be applied to any selected portion or region of a microfluidic cavity element (i.e., a channel, reservoir, chamber or device element). Gas can be delivered to and vacuum applied to one or more selected cavity elements within a microfluidic device that comprises a plurality of such cavities. To apply vacuum to a selected location or cavity, all or a portion of at least one wall of a selected cavity element in a microfluidic device is formed from a gas-permeable substantially liquid impermeable membrane (GPLI). The membrane is, in turn, in fluid communication with one or more sources of gas(es) or vacuum.

The selectively positioned membrane(s) with associated gas source or gas sources provides an internal gas delivery system for a microfluidic device. Controls external to the microfluidic device can be employed to control the type and amount of gas delivered to a given location or cavity element in a microfluidic device and/or control the time schedule or rate of delivery. The gas delivery system is readily adapted to any microfluidic device design and allows selective application of a gas to a selected portion of the device.

The selectively positioned GPLI membrane(s) with associated vacuum source provides an internal degassing system for a microfluidic device. Controls external to the microfluidic device can be employed to control the schedule for vacuum application and to control the level of vacuum applied to a given location or cavity element in a microfluidic device. The degassing system is readily adapted to any microfluidic device design and allows selective application of vacuum to a selected portion of the device.

More specifically, the microfluidic gas delivery system comprises a microfluidic cavity element formed with a plurality of walls (including top and side walls). At least a

portion of one wall forming the cavity element is a GPLI membrane. The remaining walls of the cavity element being substantially nonpermeable to fluids. The GPLI membrane has an outer surface and an inner surface (where outer and inner are defined with respect to the cavity of the cavity element). The inner surface is in contact with the microfluidic cavity of the cavity element for delivery of gas through the membrane to the cavity. A gas source, which preferably comprises a microfluidic channel, is in fluid communication with the outer surface of the GPLI membrane to deliver gas to the cavity. Gas can be applied at a plurality of locations to the outer surface of the membrane employing a gas delivery plenum.

More specifically, the microfluidic degassing system comprises a microfluidic cavity element formed with a plurality of walls (including top and side walls). At least a portion of one wall forming the cavity element is a GPLI membrane. The remaining walls of the cavity element being substantially nonpermeable to fluids. The GPLI membrane has an outer surface and an inner surface (where outer and inner are defined with respect to the cavity of the cavity element). The inner surface is in contact with the microfluidic cavity of the cavity element for passage of gas through the membrane to be removed via the vacuum source. A vacuum source is in fluid communication with the outer surface of the GPLI membrane to apply vacuum to the cavity. Vacuum can be applied at a plurality of locations to the outer surface of the membrane employing a vacuum plenum.

In a preferred embodiment, gases are delivered and vacuum is supplied to the GPLI membrane through one or more microfluidic channels formed in the microfluidic device. Microfluidic channels for gas and/or vacuum delivery are preferably distinct from any microfluidic cavity elements of the device that carry liquids. A selected microfluidic channel may, however, in one operating state deliver gases and in another operation state supply vacuum to the same microfluidic device. The use of microfluidic channels for gas or vacuum delivery allows selective delivery to one or more selected cavities of the device avoiding gas delivery or vacuum application to all cavities in the device. This is beneficial because application of a vacuum to certain device elements (e.g., a microfluidic valve or pump) can disrupt the function of the device element. Using the internal degassing device, vacuum can be applied to a microfluidic device without significant disruption of such device elements. A

further benefit of the described systems is the ability to control the amount and type of gas within a selected region or cavity element of a microfluidic device.

Gas can be delivered or vacuum applied to one GPLI membrane wall (or wall portion) of a given cavity element or more than one wall of a given cavity. Application of vacuum to more than one wall of a cavity element, particularly to opposite GPLI walls of that cavity element, provides improved efficiency of degassing. Preferred GPLI membranes are made from poly(dimethylsiloxane).

The internal degassing system can be used to facilitate wet out of microfluidic devices and is useful in combination with one or more microfluidic cavity elements having mesoscopic length and width (with dimensions greater than about 1 mm) and microscopic depth (less than about 300μm). The internal degassing system is particularly useful in combination with one or more microfluidic cavity elements that have broad, flat geometry with width/depth aspect ratios of 25 or more.

The internal degassing system can be used continuously or intermittently to remove gas bubbles from a microfluidic cavity element that might be generated during operation of a microfluidic device or device element. In an analogous manner, the internal gas delivery system can be used continuously or intermittently to introduce one or more gases into a microfluidic cavity element during operation of the microfluidic device or device element.

The exemplary internal gas delivery and degassing system of this invention can be implemented in a multiple layer laminate microfluidic device (a microfluidic cartridge) by providing gas and/or vacuum routing layers and optionally gas and/or vacuum transfer layers to the desired location(s) in the microfluidic device. Routing and transfer layers have appropriately shaped holes and directional channels formed in the layer by precision etching or more preferably by precision laser cutting to provide the desired gas delivery pattern or vacuum application pattern.

Other benefits and advantages of the interconnect seals, manifolds and gassing and/or degassing systems of this invention will become apparent on review of the following detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 A is a schematic cross-sectional view of a face seal formed between a tube and an elastomer layer. Figure 1B illustrates the cross-sectional area of a flat (non-ridged) tubing end face.

Figures 2A-E are schematic cross-sectional views of several failure modes for face seals. Figures 2D and E compare the effect of increasing force (F1<F2) on channel occulsion.

Figure 3A is a schematic cross-sectional view of a face seal formed with a tube having a ridged end face. Figure 3B is a detailed view of the tube end face with ridge.

Figures 4 A-E are exemplary interconnect tube sealing end face geometries. Figure 4A is a square ridge end face. Figure 4B is a center V-ridge. Figure 4C is a edge V-ridge. Figure 4D is an edge acute angle ridge (e.g. 30° angle with side of tube). Figure 4E is a semi-circle wave ridge

Figure 5A is a perspective view of an exemplary fluid interconnect manifold of this invention. Figure 5B is an exploded view of an exemplary fluid interconnect manifold of Figure 5A. Figure 5C is a schematic view of a face seal formed between a ridged end face tube and the elastomer layer of a multi-layer laminate microfluidic device at a microvia in the elastomer in an interconnect manifold.

Figure 6A-F illustrate fluid interconnect manifold of this invention with multilayer laminated microfluidic device inserted. Figure 6A illustrates a elastomer seal layer of a microfludic device. Figure 6B is an assembled exemplary multi-layer laminate microfluidic device (also called, a microfluidic device cartridge). Figures 6C-6F are, respectively, a top

view, bottom view, a side and front view of the interconnect manifold of Figure 5A and B with the microfluidic device of Figure 6B in place.

Figure 7 schematically illustrates a gas delivery/removal system of this invention for delivery of one or more gases or for application of a vacuum to a microfluidic cavity element.

Figure 8 schematically illustrates, in cross-section, a vacuum degassing system of this invention applied to a microfluidic sedimentation separation module. Vacuum is applied to the sedimentation channel and to the product channel. Vacuum is applied via a vacuum routing channel and distribution ribs.

Figure 9A is an exploded view of a multiple layer laminate microfluidic device with 13 layers and a top and bottom planar rigid frame. The illustrated multiple layer device has the structure of the sedimentation module as illustrated in cross-section in Figure 8 and is implemented in a flat channel (high width/depth aspect ratio) design. The illustrated layers are aligned and assembled within the frame and secured through the top frame, the layers and the bottom frame. Figure 9B is a top view of an assembled multiple layer laminate microfluidic device of Figure 9A. Figure 9C illustrates an elastomer layer that is positioned on an outer layer of the laminate device to facilitate interconnect seal formation.

Figure 10 is an exploded view of another multiple layer laminate microfluidic device with 13 layers and a top and bottom rigid planar frame. The illustrated multiple layer device has a flat channel (high width/depth aspect ratio) design. The illustrated device is an electrophoretic/isoelectric concentration module with electrodes above and below the separation channel. The electrodes are implemented as porous electrodes. A degassing system is incorporated on either side of the separation channel.

DETAILED DESCRIPTION OF THE INVENTION

In one aspect, the present invention provides means and methods for making fluid interconnects between microfluidic channels and macrofluidic or mesofluidic channels. These fluid interconnects provide a fluid interface between a microscale environment and a macro- and or mesoscale environment.

The term "micro" when used herein as in "microfluidic" refers to channels and fluid devices (valves, pumps, etc.) for storing or carrying fluids where the channel or device element (valve, pump, etc.) has at least one dimension (i.e., length, width or depth) that is less than about 500µm. Microfluidic devices, device elements (e.g., valves and pumps) and channels typically exhibit low Reynolds Numbers. Historically, the term microfluidics has evolved from the more general term "micro flow devices," where such devices were defined to be very small devices that either controlled or sensed flow in the order of microliter/min. Most microfluidic devices are characterized by low Reynolds number, non-turbulent flows. Typically such flows have a Reynolds number of less than 2000, more typically less than 100 and many have Reynolds Numbers less than 10, or even 1. Flow in at least portions of a microfluidic device is typically substantially laminar. A microfluidic device is composed of fluid channels, and/or device elements (pumps, valves, sensors, etc.) wherein at least one and typically all fluid channels and device elements are microfluidic. More specifically, microfluidic channels include those channels where at least one dimension (height, length or width) is less than about 500 µm. Preferred embodiments have at least one dimension less than 400 µm, more preferably less than 400 µm, more preferably 300 µm, more preferably 200 µm, more preferably 100 µm, and in some instances on the order of 1 µm. Preferred embodiments may have two primary dimensions in the microchannel dimension range. The terms "mesofluidic" and "macrofluidic" refer to fluid channels and fluid device elements and systems comprised of elements that are typically larger. Mesofluidic systems, or mesosystems are typically sized from the size of a sugar cube to fist sized. Macrofluidic systems, or macrosystems are larger. Devices or systems that are mesoscopic or macroscopic in size can contain microfluidic elements and as such are classified as microfluidic. Often, a microfluidic system, or mesofluidic system will have a limited lifetime and will be used in concert with a permanent instrument that has high capital cost electronics, optics, and data

processing and display capabilities. The invention described herein is compatible with such instrument systems. The invention described herein is also compatible with a multitude of hybrid electro-optical-mechanical hybrid microsystem modules.

The term "fluid" is used broadly herein to refer to liquids and gases. Fluids may vary in viscosity and may include viscose fluids, such as gels or creams. The nature and properties of the fluid are selected as is known in the art for a given microfluidic application. Fluids may contain suspended or entrained particles and may be emulsions. Fluidic channels hold, carry or transport fluids. Fluidic channels deliver sample or reagent to a microfluidic device or device element Fluidic channels also remove sample, product or waste from a microfludic device or device element. A channel to which a vacuum is applied (i.e., to remove a fluid) is a fluidic channel.

The fluid interconnect of this invention typically provides an interface between macro- or mesofluidic supply channels (sources of fluids, vacuum lines, etc.), sample or product collection channels, and channels to analytic instruments (various spectrometers, etc.) and microfluidic channels or device elements in microfluidic devices.

The invention is further illustrated by the drawings in which the same numbers in different drawings refer to like features. The terms "top", "bottom" and "side", if used, refer to the orientation of elements in the drawing referred to, which is not necessarily the orientation of the elements in operation.

Figure 1A provides a cross-sectional view of a face seal formed between a rigid tube (5) and an elastomer layer (10) of a microfluidic device. The microfluidic device (6) is illustrated as a multi-layer laminate device (with a partial cross-section of the layers shown). The elastomer layer has a microvia (7) in fluid communication (or fluid connection) with microfluidic channel (8) formed in the layers of the microfluidic device. In the face seal configuration, the tube is normal to the seal surface (the elastomer) and the tubing end face (4, i.e., the sealing end face) is perpendicular to the tubing bore (3). To form a fluid interconnect the tubing bore (3) is aligned with the microvia. The tubing bore diameter (determined by

tubing wall thickness (2)) is typically about the same size as or larger than the diameter of the microvia. The elastomer layer needed to form the seal is larger than the area of the tubing end face and is most over significantly larger. Force (F) is applied to the tubing, the elastomer or both (preferably substantially normal to the elastomer seal/ tube end face plane) to press the tubing end face against the elastomer seal layer to form a face seal. The effective seal area, A eff, is the cross-sectional area of the tube, i.e., the area bordered by the I.D. (i.e., the tube bore diameter) and O.D. of the tube, see Figure 1B. The normal stress applied is the force divided by the area of the seal (F/Aeff). The face seal approach, as illustrated, requires a maximum applied force to insure a given level of interconnect normal stress at the interface between the tube end face and the elastomer. In this seal configuration, it is important to note that if even a thin film of fluid can wedge itself between the tube end face and the elastomer, then the hydrostatic pressure of the contained fluid can be experienced by the entire interconnect end face. If a perfectly square tubing end face is engaged perfectly with the elastomer layer, this seal geometry works. However, this is rarely achieved in practice and face seal strength is very sensitive to minor interconnect (tube or end face) to seal registry perturbations.

Figures 2A-E illustrate several failure modes for face seals of Figure 1. Figure 2A illustrates the case where the tubing delivery mechanism is not aligned perpendicular to the elastomer seal (i.e., the tube axis is not normal to the elastomer layer). This may be caused, for example, by poor hardware registry and/or by uncontrolled flexure in the interconnect tubing and/or poor planarity of the elastomer layer in the microfluidic device. To achieve a complete seal over the entire seal area in this failure mode requires over compression of the seal. The resulting seal can readily fail because it will have an uneven distribution of interfacial stress around the seal, with large interfacial normal stress on one side of the seal and a much smaller stress on the other. Figure 2B illustrates a similar seal failure mode where the tube end face (4) geometry is not square (i.e., the end face is not parallel to the elastomer surface). Again there will be non-uniform circumferential stress distribution for a given applied force which will weaken the seal and make it susceptible to failure. Figure 2C illustrates a generic failure mode in which the end face (4) geometry is irregular.

Figure 2D and 2E illustrate the result of over compression in a face seal of Figure 1. Figure 2D illustrates partial microvia occlusion (7) and Figure 2E illustrates complete microvia (7) occlusion. In the illustrated face seals, the sealing action is distributed over the maximum area

and as such more force is required in general to insure adequate interfacial seal stress at all locations circumferentially around the interconnect tube. Minor occlusion as illustrated in Figure 2D can be tolerated, however complete microvia occlusion (and seal failure) will result, if more force is applied to increase the barreling of the seal material. Over compression is commonly associated with the failure modes due to irregular tube alignment or geometry. In such cases, a seal leak occurs and additional force is applied to fix the leak which can lead to over compression of the seal material and barreling of the microvia. It might be considered that simply making the microvia larger would solve the problem with occlusion. However, this solution is not desirable because it is preferred in a microfluidic system to minimize dead or unswept volumes.

In one embodiment, this invention provides improved tube end face geometries that decrease the occurrence of seal failure in face seals between a rigid tube and an elastomer seal layer. The sealing end face of the tube is provided with one or more ridges which function to lock-in the position of the tube with respect to the elastomer, minimize barreling of the elastomer to close the microvia, significantly increase localized stress in the elastomer in the critical seal regions, and/or significantly increase the achievable seal engagement depth between the tube end face and the elastomer in the critical seal region. The use of ridged seal end faces generates stronger seals which are less sensitive to minor perturbations in tube normality and irregularities in tube end face geometry.

Figure 3A is a schematic cross-sectional view of a face seal formed with a tube (5) having a ridged end face. The sealing end face of the tube (11) is provided with a square ridge (12) extending circumferentially around the perimeter of the tube (an edge-positioned square ridge). The ridge extends a selected height (14) from the end of the tubing bore (15) and has two walls an outer wall (16, toward the perimeter of the tube) and an inner wall (17, toward the perimeter of the tubing bore) and a top surface (18) of selected width (19), as

illustrated in Figure 3B. In the illustrated case, the walls of the ridge are parallel to each other and the top of the ridge is perpendicular to the walls to form the square ridge. The ridge may be positioned anywhere between the perimeter of the tube and the perimeter of the tubing bore, but is preferably positioned at the tube perimeter or between the tube perimeter and the perimeter of the bore, rather than at the perimeter of the bore. Positioning of the ridge at the bore requires careful machining and alignment to insure that the ridge engages the elastomer. However, in a specific embodiment, the ridge can be sized, shaped (typically round) and positioned to engage the microvia in the elastomer. In this case the ridge extends into the microvia to prevent its closure on compression to form the seal.

The ridge illustrated in Figures 3A and 3B is formed at the edge or perimeter of the tube and the outer wall of the ridge is the outer tube wall, i.e., the outer ridge wall extends from the tube perimeter. In a ridge positioned at the bore perimeter, the inner wall of the ridge extends from the tubing bore perimeter. The width (19) of the square ridge is less than the tube wall thickness (2), preferably less than about ½ of the wall thickness and more preferably less than about 1/4 of the tube wall thickness. Tubes are typically round with round bores, as illustrated, in the Figures herein. In this case, end face ridges are generally circular extending around the tubing ring that is the tubing end face. Fluid interconnect tubes and bores may have other geometries (e.g., oval, square, etc.) and the shape of the bore perimeter need not be the same as the perimeter of the tube (e.g., a square bore in a round tube). In these cases the path of the ridge or ridges on the end face may take the shape of the perimeter of the tube or of the bore.

The presence of the ridge or ridges at the tubing end face decreases the seal area and focuses stress from applied force such that a much higher interfacial stress can be achieved with a much lower applied force than required for a flat tubing end face. The presence of ridge(s) at the tubing end face and particularly at the perimeter of the tube also greatly reduces barreling of the microvias in the elastomer.

Figures 4 A-E are exemplary interconnect tube sealing end face ridge geometries. Figure 4A is a square ridge end face as illustrated in Figure 3A. Figures 4B and C illustrate

V-ridges (i.e., V-shaped ridges). The walls of a V-ridge (16) and (17) are sloped toward each other to come to a point at the top of the ridge (18) at a selected height (14) above the end of the tubing bore. The point of the V-ridge can, for example, be positioned intermediate between the inner and outer tube walls (e.g., the centered V-ridge with the point of the ridge positioned half the distance between the inner and outer tube walls). The V-ridge point can be posited at the tubing edge with the outer ridge wall sloping up from the outer tubing wall toward the bore (as illustrated in the edge V-ridge of Figure 4C). The V-ridge of the can also be positioned at the inner edge of the tubing with the inner wall of the ridge sloping up from the inner tubing wall toward the outer wall of the tube. One of the walls of the ridge can be sloped to form a point at the top of the ridge. Figure 4D illustrates an outer edge-positioned acute angle ridge (12) where the inner wall of the ridge is sloped and the outer wall is perpendicular to the outer tubing wall (e.g., the illustrated ridge slopes toward the outer edge of the tube making an acute angle of about 30° with outer wall of tube which forms the outer wall of the ridge). The point of the acute angle ridge can be positioned intermediate between the inner and outer wall of the tube. The point of the ridge or the edges of the square ridges may also be rounded. Each of the end face ridges illustrated in Figs. 3A and 4A-D follow or trace a circular or round path around the end face which is symmetric with respect to the tubing bore. Ridges on the end faces may trace more convoluted, yet symmetric paths or may trace asymmetric paths on the end face. In any event the ridge, must circumlocate the tubing bore so that a complete face seal can be formed.

The sealing end face of the tube may contain more than one ridge of the same or different heights. However, a given ridge preferably maintains the same height along its path around the bore to insure uniform seal formation. For example, the top of a ridge may be indented to form multiple square or rounded ridges. Alternatively, one or both walls of the ridge may be stepped, indented, or otherwise shaped to provide additional pointed, souare or rounded ridges. Figure 4E illustrates a multiple ridge geometry. In this case a semi-circle wave geometry is imposed on a square ridge to generate two rounded ridges.

The selection of the number and geometry of ridge(s) on the sealing end face will, at least in part, depend upon the properties of the mating elastomeric seal. For example, the

square geometry of the ridge of Figure 4A is preferred for use with a more pliable elastomer, such as poly dimethylsiloxane (PDMS), urethanes (e.g., 60A urethane), or latex rubber. Whereas a "biting" geometry, like those having a pointed ridge top (Figures 4B-D) are preferred for use with more rigid seal materials, such as shore 80A Buna-N-rubber. Elastomer materials exhibiting higher shore A hardness values are generally more rigid. The selection of the type of ridge also depends in part of the application and whether or not it is intended to reuse the elastomer seal. For example, the use of a "biting" geometry, such as a V-ridge may form a stronger face seal with a given material, but its use may decrease the useful lifetime of the elastomer which may be a layer in a laminated microfluidic device.

The ridge (12) on the end face (4) of the interconnect tube is intended to compress and engage the elastomer. The height of the ridge (14) is selected to achieve a desired seal engagement depth which may be adjusted to achieve desired seal properties (e.g., seal strength, seal durability, seal reusability, etc.). The height of the ridge is less than the thickness of the elastomer layer. In preferred embodiments, the ridge height is equal to or less than about ½ the elastomer thickness and more preferably equal to or less than 1/4 of the elastomer thickness. In microfluidic devices illustrated herein ridge heights of 5-20 thousandths of an inch have been used successfully to form face seals.

A ridged end face geometry can be readily selected for use in a given application with a given elastomer seal material by routine experimentation, for example, by pressure testing of seals formed by application of a selected force to a selected elastomer and tube end face geometry. Experiments can also be performed to assess the durability and reusability of a given seal elastomer with a given ridge geometry. Preferred seals are those that exhibit no substantial leakage up to about the maximum pressure that can be applied to the microfluidic device before massive structural failure. Seals that exhibit no leakage at pressures greater than about 50 psi are preferred for use with microfluidic devices. Seals that exhibit no leakage at pressures greater than about 25 psi are useful in microfluidic devices.

Face seals as illustrated herein are used to form fluid interconnects to a microfluidic channel. The rigid tube (illustrated in Figures 1-4) has a bore that is a macrofluidic channel

which can be used to provide a fluid connection to a macro- or mesofluidic device element or device. The dimension of the tube is typically varied by varying the bore diameter. The rigid tube provides a conduit for delivery of fluids to or removal of fluids from a microfluidic channel (typically within a microfluidic device). The interface of the microfluidic device is typically formed by introducing a microvia (7) in an elastomer seal top or outer layer (10) of the device. The elastomer seal layer may extend over all or a portion of the top or outer layer of the device. A microfluidic device may have multiple elastomer seal layers on the same or different surfaces, which access the same or different microchannels in the device. A given microfluidic device may have multiple seals made of different elastomers. In a multiple layer laminate microfluidic device, elastomer layers may be positioned on different layers. A microvia is formed in the elastomer as is known in the art, for example by precise (to 1- 2 thousandths of an inch) laser cutting of the elastomer. A microfluidic channel or device element (e.g. a valve) is in fluidic communication with the microvia, either directly or via a mesofluidic channel or device element. In a multiple layer laminate device, the layer or layers under the elastomer form a microfluidic channel or device element and the microvia is in fluid communication with the microfluidic channel or device element.

Various methods are known in the art for creating microfluidic devices containing microfluidic channels and device elements. In a preferred embodiment, the fluid interconnects of this invention are employed with microfluidic devices, also called microfluidic cartridges, formed as multiple layer laminates. A multilayer laminate is formed as is known in the art by providing structural features, channels of varying dimensions and shapes, fluid storage chambers, fluid routing schemes, e.g., distribution channels, and device elements, such as valves in overlaid layers, which are held in desired relative alignment in a rigid support frame (e.g., made, for example, of acrylic or other rigid plastic or an appropriate metal, such as stainless steel) Exemplary multiple layer laminate microfluidic devices are illustrated in the exploded views of a multiple layer sedimentation device of Figure 9A and the electrophoretic/isoelectric focusing device of Figure 10.

A given microfluidic device can have one or more fluid inlets or outlets (each formed with a microvia in an elastomer) each of which may be formed in the same elastomer layer or

in different elastomer layers and the material used in different elastomer layers may be the same or different.

A face seal is formed by positioning the interconnect tube (5) such that the bore of the tube (3) is aligned with a microfluidic via (7) of the elastomer seal layer (10) and such that the end face of the tube (4) is in contact with the planar elastomer seal layer of the microfluidic device. Sufficient force is applied to the tube and/ or the microfluidic device substantially normal to the tube end face and elastomer layer to form a complete seal. The force applied is preferably sufficient to form a complete face seal that will exhibit no leakage on application of a pressure of 25 psi or greater in a pressure test of the seal. More preferably, the force applied is sufficient to maximize seal ridge engagement depth (preferably the entire ridge and its walls engage the elastomer) and bring the elastomer into mating contact with the flat (non-ridged) areas of the tubing end face.

Force can be applied to either or both the tube and the elastomer (e.g., by applying force to the microfluidic device carrying the elastomer) and is substantially normal to the end face and elastomer sealing surface. The interface components (tube with end face ridge(s), elastomer and microvia) are typically clamped together to form the face seal. In a preferred embodiment, the interface components are sealed together in a multiple interconnect manifold that provides for a plurality of interconnects to one or more microfluidic devices.

The fluid interconnects of this invention can be formed using an interface manifold as illustrated herein. The manifold of this invention provides for the formation of interconnects with one or more fluid inlets or outlets in one or more microfluidic device. The manifold provides for selective relative positioning of one or more interconnect tubes with microvias of one or more microfluidic devices. The manifold also provides for application of force simultaneously to more than one interconnect face seal.

Figure 5A provides a perspective view of an exemplary fluid interconnect manifold (100) of this invention. The illustrated manifold consists of a manifold body (102), a strain relief element (105) and a clamping mechanism (110). The manifold body and the strain

relief element have a plurality of selectively positioned cavities each for receiving one of a plurality of interconnect tubes (103). The strain relief element is mounted (e.g., detachably mounted with screws(107)) on the manifold body with strain relief element tube cavities 104 and manifold body tube cavities 106 (shown in Fig. 5B) aligned. A tube (103) enters a cavity on the strain relief element (104) and passes through the tube cavity (106) in the manifold body. The tube has a bore that is microfluidic. A locking element (111) selectively locks a tube in place in a cavity. The locking element in the exemplified manifold comprises a strain relief collar (112) (shown in Figure 5B) and a set screw (113). The length that each tube extends from the bottom of the manifold body can be adjusted prior to locking a tube in place. Clamp frame (120) is indirectly attached to the manifold body via a clamp offset element (119). A clamp pad (114) is cooperatively linked to the clamp frame and moveable between the frame and the bottom surface of the manifold (117) by adjusting screw (121). The clamp pad (114) and the manifold body (102) form a cavity (125) for receiving a microfluidic device. The manifold body has a plurality of alignment or registry pins (122) extending from its bottom surface. A microfluidic device having registry holes is introduced into the clamp cavity in appropriate orientation to engage the registry pins (122) in the registry holes (not shown).

Figure 5B provides for detail of the exemplary manifold of Figure 5A. In this exploded view, the tube cavities in the manifold body (106) can be seen. Further, the components of the locking element can be seen. There is a strain relief collar (112) in each tube cavity of the strain relief element (105). A set screw (113) is provided in a threaded hole (114) that enters the tube cavity of the strain relief element. Tightening the set screw in the threaded hole, applies lateral force to the collar (112) which deforms to lock a tube (103) in the tube cavity. Although not visible in the drawing the ends (123) of each tube protrudes from the bottom surface of the manifold. The distance that each tube protrudes can be selectively adjusted prior to locking the tube in place. The set screw mechanism for locking illustrates a selectively adjustable lock. However, tubes can be locked in place by any mechanical or adhesive means, for example, the tubes may be locked in place with glue or epoxy.

The microfluidic device clamp is illustrated in more detail in Figure 5B. The clamp cavity(125) is shown between the clamp pad and the bottom of the manifold. The clamp pad is slidably engaged with the clamp frame via two clamp guides (128). Tightening screw (121) in threaded hole (129) exerts upward force on the clamp pad to raise or lower the pad with respect to the manifold bottom (117). When a microfluidic device, is positioned in the clamp cavity with registry pins engaged and elastomer layer facing upward opposite the manifold body, the screw (121) is tightened to raise the microfluidic device and bring the elastomer layer into contact with the bottom of the manifold body and the protruding tube ends. The clamp is tightened to form a complete seal between the end faces of all of the interconnect tubes and the elastomer layer(s) on the microfluidic device.

Fig[illegible]tes the formation of a face seal between a seal end face and an interconnect tube in the manifold of Figures 5A and B. The tube illustrates in this figure has a ridged end face. The tube protrudes from the bottom of the manifold. The length of protrusion (P) from the top of the ridge to the plane of the end face having the bore opening is adjustable as desired, but is illustrated as about the equal to the height (114) of the ridge present on the end face. Microfluidic device (6), shown as a multiple layer laminate, has an elastomer layer (10) with a microvia (7) in fluid communication with a microfluidic channel(8). The device is clamped between the manifold bottom surface (117) and the clamp pad (114). In the figure, the clamp has been adjusted to bring the elastomer into contact with the tube end face. In general, sufficient force (F') is applied to achieve a seal of desired strength, as noted above. When a ridged end face tube is used, force is preferably applied through the clamp until a maximum seal engagement depth is achieved (i.e., the end face ridge fully engages the elastomer) and the non-engaged elastomer comes into flat facial contact with the bottom surface of the manifold.

The manifold is illustrated with a tube having an end face ridge. Tubes without end face ridges can be employed in the manifold as well. Another seal configuration, not specifically illustrated, employs a tube with a ridge at the bore perimeter that is sized and aligned to enter the microvia in the elastomer. Such a configuration insures that the microvia remains open on compression, but the use of this configuration requires very precise

machining of the ridge matched to the microvia and very precise alignment of the microvia and the tube.

Precise alignment of the tubes is obtained by formation of very precise tube cavities in the manifold body. These tube cavities are formed to a precision of about 1-2 thousandths of an inch to provide a very close sliding fit with the interconnect tube. The tube cavities in the strain relief cavity are sized to accommodate the strain relief collar which in turn is sized to receive the interconnect tube.

As noted above, the tube end face extends or protrudes from the manifold body tube cavity at the bottom surface of the manifold (distance P). The length of the tube protrusion can be individually set for each tube in the manifold. It may be desired to have increased or decreases lengths for different tubes. For example, it may be desired to increase the stress at one or more selected interconnects in the manifold which can be achieved by increasing the protrusion length of the selected tubes. When the microfluidic device is clamped into the manifold with a given force, tubes with longer protrusion (assuming that the elastomers are at the same layer in the microfluidic device) will impose higher local compression (and more local stress) on the elastomer that they contact. In the illustrated manifold, for use with multiple layer laminate microfluidic devices protrusion lengths ranging from about 5-20 thousandths of an inch have been used. As noted above, it is generally preferred to adjust the protrusion length of the tube to the end face ridge height. Precise adjustment of tubing protrusion can be accomplished using a set of custom jigs that are inserted into the clamp cavity of the manifold and clamped in facial contact with the bottom surface of the manifold body. A tube is inserted into the manifold body via the stress relief element with the desired jig in place to come to a hard stop against the jig. The tube is then locked in place by tightening the set screw or applying another locking mechanism.

An exemplary face seal formed between a square ridged tube (as in Figure 5C) and a 0.010" latex rubber seal in the manifold device of Figures 5A and 5B withstood a pressure test in excess of 100 psi. In this use PEEK tubing carrying a 0.005" high, 0.015" wide ridge was used.

Figures 5C-F illustrate fluid interconnect manifold of this invention with multilayer laminated microfluidic device (130) inserted in the manifold clamp. Figure 6B is an exemplary assembled multiple layer laminate microfluidic device (130) (also called, a microfluidic device cartridge) with an elastomer seal (10) and a plurality of microvias (7) on the seal layer. Registry pin holes are illustrated in the device (133) at the elastomer layer which extended through the device. Figure 6A illustrates a elastomer seal layer of the microfludic device of Figure 6B again illustrating microvias (7) and registry holes (13). Figures 6C-6F are, respectively, a top view, bottom view, a side and front view of the interconnect manifold of Figure 5A and B with the microfluidic device of Figure 6A in place.

The function of the microfluidic device (113) illustrated in combination with the manifold is unimportant in the context of this embodiment. One or more elastomer seals (10) may be mounted in any appropriate location on such a device for use with manifolds of this invention.

The manifold is illustrated with nine interconnect tubes (103) in a linear array. A manifold is readily constructed to accommodate more or less interconnect tubes and the manifold body can be readily modified to any array geometry. Interconnects are shown on one surface of the microfluidic (e.g., a top surface), but can be provided on different surfaces of the microfluidic device (e.g., a bottom surface). The interconnects are illustrated on one side of the top surface, but may be provided on any point on a surface of the microfluidic device e.g., interconnects can be provided at both sides of the top or bottom surface or near the center of a surface.

In Figures 5A and B, the manifold body, strain relief element, clamp frame and clamp offset are illustrated as selectively detachable (attachable to each other with screw fasteners). These parts of the manifold can be formed in as a unitary body by means known in the art. The shape and size of the clamp and manifold can be readily adapted for use with any microfluidic device. The manifold can be readily adapted for use with different types and sizes (either different O.D. or I.D.) Of tubes. Exemplary manifolds employ rigid PEEK (polyetheretherketone) tubing (Upchurch) which is available in a variety of sizes.

The clamping mechanism illustrated in achieved by tightening a screw. Alternate mechanical, electromechanical, and pneumatic clamping means can be employed to apply a desired force to the elastomer and the tube end face to form the face seal. The force applied by the clamp can be monitored and/or controlled for reproducibility.

In a second aspect of the invention, devices and methods for internal delivery and removal of gas from microfluidic devices is provided.

Figure 7 is a schematic drawing of a cross section of a microscale channel system for delivery or removal of gases from a microfluidic cavity element (150) with fluid inlet (151) and fluid exit (153). The direction of fluid flow in the cavity is shown by an arrow in the figure. The upper wall of the channel is formed from a gas-permeable, substantially liquid impermeable planar membrane (155). A microfluidic supply channel (157) is in fluid communication with a plurality of slots (159) which extend to the outer side of the membrane (156). In the illustrated system only one wall contains a GPLI membrane, the other walls that form the cavity are substantially impermeable to gases and liquids. In alternate embodiments, both the top and bottom (as illustrated in the drawing) walls of the cavity (e.g., opposite walls of the cavity) can be formed from GPLI membrane. This configuration provides for improved degassing efficiency.

When the system is employed to deliver gas to the cavity, the supply channel 157 is connected to one or more gas sources. Valves and gas flow control can be provided external to the microfluidic device. When gas is introduced into the supply line, it is distributed through slots 159, passes through the GPLI membrane and enters cavity 150. When the system is employed for degassing, the supply channel 157 is connected to a vacuum supply, such as a vacuum pump. Valves can be provided external to the microfluidic device and vacuum pressure applied can be controlled externally. When vacuum is applied to supply channel 157, it is distributed by the slots 159 to the membrane to remove gases from the channel and from liquid in the channel.

In a given device, the same supply channel can be used to apply vacuum and to supply gases, but not at the same time. Control valves can be provided external to the microfluidic device to switch between gas flow and vacuum. For example, vacuum can be applied to facilitate system wet out, and thereafter, with the vacuum switched off or diverted, a gas can be supplied to the degassed cavity through the supply channel.

Figure 8 is a schematic drawing of the cross-section of a sedimentation separation module (200) employing a degassing system of this invention. The operation of the sedimentation device illustrated is described in M. R. Holl, K. Macounova, and P. Yager (2000) *Micro Total Analysis Systems 2000* pp. 319-322 (A. van den Berg et al., eds.) Kluwer Academic Publishers, which is incorporated by reference in its entirety herein. The module functions to separate particles by size and density and its operation is based on the principles of sedimentation field flow fractionation. The module has a main sedimentation cavity 205 with an upper (201) and a lower (202) wall. Sample is introduced into the cavity at inlet 151. A product collection channel 207 is in fluid communication with the sedimentation channel at its upper wall at a selected distance R from the sample inlet. The sedimentation cavity, as illustrated, is operated with the cavity at an incline (illustrated at 45° from horizontal). The sedimentation length is determined based on the incline angle, liquid flow rate and the characteristics of the particles to be separated, as is discussed in Holl et al. (2000) supra. The length of the sedimentation cavity is typically selected to be longer than the sedimentation length (preferably about 2-3 times longer). Liquid containing a mixture of particles flows along the length of the sedimentation cavity (L) and the particles are separated by size and density. Smaller, less dense particles rise in the liquid flow towards the upper wall of the sedimentation cavity and flow into the product collection channel 207. Larger, denser particles do not rise and ultimately remain in the sediment sump 208 at the end of the sedimentation cavity. Separated product can be removed from the module at product exit port 153. Separated product may flow into another functional microfluidic device after leaving the sedimentation module.

The lower wall of the sedimentation cavity is formed from GPLI membrane 155a and vacuum is applied to the backside of the membrane through a plurality of slots (159a) in fluid

communication with vacuum supply line 157a. The upper wall of the product collection channel is formed from GPLI membrane 155b and vacuum is applied to the membrane through a second vacuum supply channel 159b and a second set of slots 159b. Vacuum supply lines 159a and b may converge at a single vacuum inlet to the device or may be supplied independently. Application of vacuum to the sedimentation cavity and the product channel during operation of the sedimentation module did not adversely affect device function for particle separation.

A variety of materials can be used as GPLI membranes. GPLI membranes suitable for use in the devices of this invention can be made of any material that is permeable to gases and substantially impermeable to liquids, such as water or aqueous solutions. Suitable membranes include semipermeable or microporous polymeric membranes, such as those formed from polydimethylsiloxanes (PDMS), polyurethanes, polyolefins (including polyethylenes, polypropylenes, ethylene propylene polymers, and phenolic polyethylenes), polytetrafluoroethylenes (TFE), fluorinated ethylene propylene (FEP) or polysulfones. A variety of appropriate GPLI polymeric materials are commercially available (e.g., PTFE materials available as Mupor™ (Porex Corp., Fairburn GA), or can be prepared by methods known in the art or by routine adaptation of well-known methods. Micro- and nanoporous solids, such as hydrophobic nanoporous silicon, can also be employed as GPLI membranes. Nanoporous silica is described in U.S. patents 6,022,812; 6,037,275; 6,045,677; 6,048,804; 6,054,206. Hydrophobic nanoporous silica is described in published International applications: WO 00/13222 (March 3, 2000) and WO 00/44036 (July 27, 2000). All of these U.S. patents and published International applications are incorporated by reference herein for their teachings concerning nanoporous silica and hydrophobic nanoporous silica. Since most microfluidic device applications employ water or aqueous solutions, preferred membranes are hydrophobic and substantially impermeable to water. PDMS membranes are presently preferred for degassing applications. Spun cast PDMS membranes (0.20 inch thick) were found to provide significantly faster degassing in multiple layer laminate devices compared to PTFE membranes of comparable thickness. PDMS membranes (0.020" thick) were prepared by spin casting of Sylgand 184 (Dow Corning) 10 parts silicone elastomer to 1 part curing agent by weight. PDMS membranes have higher gas permeabilities than comparable

thickness PFE membranes. Membranes with higher gas permeabilities are generally preferred for use in degassing applications. For gas delivery applications high permeability membranes are also preferred. However, it may be desirable in a given application to select a lower permeability to achieve selective gas introduction.

The gas delivery/removal system of this invention is readily implemented in multiple layer laminate microfluidic devices, such as those described in published international application Holl et al. WO 99/60397 and pending U.S. patent application 09/428,804 filed Oct. 28, 1997. Figure 9A is a perspective exploded view of a sedimentation module, as illustrated in Figure 8, implemented in a 13 layer laminate assembled between a top (201) and bottom (203) acrylic frame. The assembled device 200 is illustrated in Figure 9B. Note that the exploded device in the Figure 9A is inclined as it would be in operation. In such devices the layers are Mylar or adhesive-carrier-adhesive laminates (ACA), where the adhesive is a pressure sensitive adhesive, design features are etched or more preferably laser cut into the layers and device elements, such as channels or cavities, are formed on assembly of the layers into a laminate. Mylar and ACA layers and the frames are typically provided with registry holes which facilitate alignment of the layers for assembly. Preferred ACA layers are pressure sensitive adhesive (e.g., 3M-1151 adhesive (produced by 3M)) on a Mylar carrier. In the following discussion of Figure 9A, reference will be made to the device features illustrated in Figure 8.

Starting near the center of the layers, the sedimentation cavity is formed in an ACA layer 210 between a ribbon splitter layer 212 and a GPLI membrane 211 (0.02 inch thick spun cast PDMS was used) and a vacuum plenum layer 213 (Mylar) at the outer surface of the membrane. The ribbon splitter layer has a slot (215) cut to form the connection between the product collection channel() and the sedimentation cavity(). The product channel is formed from a cavity (216) laser cut into ACA layer 214. A routing channel 217 from the product channel to an exit channel is also provided in layer 214. The product channel is formed with layer 214 between ribbon splitter layer 212 and a second GPLI membrane 218 which conforms in shape to the product channel cavity in layer 214. A second vacuum plenum layer (219) is positioned at the outer surface of the membrane. The vacuum plenum layers have a

plurality of holes or slots (220) extending through the layer and distributed over the area of the layer that will contact the GPLI membrane. Vacuum transfer layers 221 and 222 are positioned adjacent the vacuum plenum layers. The outer surface of the vacuum transfer layers has a row of hole extending into the layer (see outer layer of layer 222) and the inner surface of the vacuum transfer layer, as shown on the inner surface of layer 221, has a plurality of slots (223) in fluid communication with at least one hole on the outer surface of the layer. The slots function for distribution of the vacuum over the area of the plenum. Upper and lower vacuum routing channel layers (224 and 225) are positioned adjacent the vacuum transfer layers. The channels in the routing layers are aligned with the holes on the outer surface of the vacuum transfer layers and extend to the side of the layer to a vacuum inlet port. A top and bottom Mylar capping layer (226 and 228, respectively) finish the layer assembly. The routing channels are formed between a vacuum routing layer and a capping layer. An elastomer layer (230) with microvias (7) illustrated in Figure 6B is bonded to the upper cap layer (226) via a seal attach layer. As described above the elastomer provides for the formation of interconnects to fluid channels. The layer assembly can be secured between the top and bottom frame with clamps, screws or other appropriate fasteners, illustrated in Figure 9B. Assembly of the layers of the device provide the internal structure as illustrated in Figure 8.

Figure 9B is a top view of the assembled multiple layer laminate device (250) of Figure 9A. In this view the elastomer is removed to show the various input and exit ports from the device. Various internal channels are illustrated in this view. Sample input 260, product output 261, and sediment output 262 connect respectively to channels 263, 264, and 265. Vacuum inlet 266 connects to both of channels 267 and 268 to supply vacuum to both GPLI membranes. This figure provides a view of the width W and length (L) of the device. The device is broad and flat with length and width in the mesoscopic range and depth (i.e., cavity depth, the distance between the layers that form the cavities) in the microscopic range less than or equal to 300 μm (with typically depths between about 100-300 μm).

Vacuum is applied to the sedimentation cavity and the product channel to facilitate wet out of the device. The degassing system of this invention is particularly useful in wet out

of devices with cavities elements having high width/depth aspect ratios. The system is particularly useful for cavity elements having aspect ratio greater than or equal to about 25. Broad, flat microfluidic device can have width/depth aspect ratios ranging from about 25 to several hundred. Device wet out, in general, becomes more difficult as the aspect ration increases above 25.

Figure 10 illustrates an exploded view of an electrophoretic/isoelectric module which has a degassing system of this invention (300). In the illustrated device, vacuum is applied to the upper and lower walls of the electrophoretic/isoelectric separation chamber. A broad, flat separation chamber is formed by combining layers 301-303. These layers provide the upper (302) and lower (303) separation chamber and the intervening splitter plane (301). The separation chamber is formed between electrode layers 304 and 305. Porous electrodes (307 and 308) are prepared by sputtering gold on to a plenum layer. The electrode layers are porous to gases and liquids. A plenum layer has a distribution of holes or slots through the layer and which in this case are distributed over an area matching the area of the separation chamber. Gold is sputtered on both sides of the plenum without obstructing the passages through the layer. Electrical connections are provided for application of voltage to the electrodes.

The remaining layers of this device are similar to those in the device of Figure 9A. A GPLI permeable membrane (309 and 310) covers the outer surface of the porous electrode and vacuum is supplied to the membrane via vacuum transfer layers (311 and 312) and vacuum routing layers (313 and 314) and Mylar cap layers. An elastomer layer can be attached to the upper Mylar cap layer with an adhesive seal attach layer to provide for seals to input and output ports on the device, as discussed above.

Microfluidic devices incorporating the internal gas delivery and/or degassing systems of this invention can be employed in combination with the fluid interconnect and interconnect manifold devices of this invention. For example, the multiple layer laminate microfluidic sedimentation device illustrated in Figure 9B is provided with an elastomer layer over the sample input, vacuum inlet, product output, and sediment output ports with microvias

aligned with the ports. Registry pin holes are also provided in the illustrated device. The device is inserted into the clamp of the manifold as illustrated in Figures 6C-6F with the elastomer seal facing towards the bottom of the manifold body to engage registry pins extending from the body. Interconnect tubes are provided in the manifold for each of the active inlets and outlets. The protrusion distance of each of the interconnect tubes is selected and the tubes are locked into position. When the clamp is tightened, face seals are formed with the inlet and outlet microvias. Samples are introduced and vacuum is applied through the appropriate interconnect tubes. Product and sediment can be extracted from the device through the appropriate interconnect tubes. In an analogous manner, an electrophoretic/isoelectric concentration module assembled from the layers illustrated in Figure 10 can be employed in combination with the fluid interconnect module of this invention.

Those of ordinary skill in the art will appreciate that device configurations, materials and procedures other than those specifically disclosed herein can be readily applied or readily adapted without undue experimentation for the practice of this invention as broadly described herein. For example, the multiple laminate microfluidic devices of Figures 9A , 9B and 10 are illustrated for degassing of one or more microfluidic cavity elements. Analogous GPLI membranes and supply microfluidic channels as illustrated in these figures can be used as gas transfer and gas distribution channels for delivery of selected partial pressures of gases to selected microfluidic cavity elements.

All references cited herein are incorporated by reference herein to the extent that they are not inconsistent with the disclosure herein.

We claim:

1. A fluid interconnect in a microfluidic device which comprises a face seal between

(a) a rigid tube having a bore which is a microfluidic channel and a sealing end face having one or more ridges of selected height positioned symmetrically around the perimeter of the bore between the perimeter of the bore and the perimeter of the tube or at the perimeter of the tube; and

(b) a planar elastomer seal layer in a microfluidic device having an upper sealing face and one or more microfluidic vias extending from the upper sealing face through the elastomer seal layer and in fluid connection with a microfluidic channel in the microfluidic device;

wherein the sealing end face of the rigid tube is positioned and held in contact with the upper sealing face of the elastomer seal layer such that the bore of the tube is aligned with a microfluidic via of the elastomer seal layer and such that the force applied is sufficient to form a complete seal around the perimeter of the tubing bore.

2. A fluid interconnect which comprises:

(a) a rigid tube having a bore which is a microfluidic channel and a sealing end face having one or more ridges of selected height positioned around the perimeter of the bore between the perimeter of the bore and the perimeter of the tube; and

(b) a microfluidic via formed in a planar elastomer layer extending from an upper sealing face of the elastomer layer through the layer and in fluid connection with a microfluidic channel;

wherein the sealing end face of the rigid tube is positioned and held in contact with the upper sealing face of the elastomer layer such that the bore of the tube is aligned with the microvia and wherein the force applied to hold the sealing end face of the tube in contact with the elastomer layer is sufficient to achieve a complete seal around the tubing bore.

3. The fluid interconnect of claim 1 wherein the force applied maximizes the seal engagement depth of the ridge in the elastomer.

4. The fluid interconnect of claim 1 wherein the force applied is sufficient to generate a seal that can be pressurized to at least about 25 psi.

5. The fluid interconnect of claim 1 wherein the sealing end face of the interconnect tube has a single square ridge.

6. The fluid interconnect of claim 1 wherein the sealing end face of the interconnect tube has a single V-ridge.

7. The fluid interconnect of claim 6 wherein the V-ridge is positioned at the perimeter of the tube.

8. The fluid interconnect of claim 1 wherein the elastomer layer is latex rubber.

9. The fluid interconnect of claim 1 wherein the microfluidic device is a multilayer laminate device.

10. A fluidic interconnect manifold for establishing one or more fluid connections to one or more microfluidic channels formed in one or more microfluidic devices, wherein a microfluidic device has al least one planar elastomer layer having one or more microvias extending through the elastomer layer each of which is in fluid communication with a microfluidic channel, which comprises:

a. a plurality of rigid interconnect tubes each having a microfluidic bore there through and a first end of the tube having a sealing end face;

b. a manifold body having a top and bottom surface and a plurality of tube cavities extending through the body from the top to bottom surface of the manifold each cavity for receiving an interconnect tube such that the first end of the tube having a sealing end face extends through the manifold a selected distance;

c. a tube position lock for each tube cavity for selectively securing a tube within a tube cavity and selectively adjusting the distance that the tube end extends from the manifold body; and

d. a selectively adjustable clamp cooperatively attached to the manifold body for receiving a microfluidic device so that the planar elastomer layer of the microfluidic device is positioned with respect to the interconnect tubes extending from the manifold body so that one or more microvias in the elastomer layer are each aligned with the bore of an extending interconnect tube and for adjusting the force of a face seal formed between the sealing end face of the tube and the elastomer layer.

11. The manifold of claim10 wherein the sealing end face of the firs t end of the rigid interconnect tubes have one or more ridges of selected height positioned symmetrically around the perimeter of the bore between the perimeter of the bore and the perimeter of the tube or at the perimeter of the tube.

12. The manifold of claim 11 wherein the sealing end face of the interconnect tubes has a single square ridge at the perimeter of the tube.

13. The manifold of claim11 wherein the sealing end face of the interconnect tubes has a single V-ridge at the perimeter of the tube.

14. The manifold of claim 10 for use with microfluidic devices provided with one or more registry holes extending at least through the elastomer layer for receiving registry pins wherein the manifold body has one or more registry pins extending from its bottom surface for engaging one or more registry holes in the microfluidic device when the microfluidic device is inserted into the adjustable clamp.

15. The manifold of claim 10 wherein the tube position lock comprises a set screw which extends into the cavity and on tightening applies lateral force to lock the position of a tube in the cavity.

16. The manifold of claim 10 further comprising a strain relieve collar selectively secured to the top surface of the manifold body and having a plurality of strain relief cavities each for receiving an interconnect tube, the strain relief cavities of the strain relief collar are aligned with the tube cavities of the manifold body.

17. The manifold of claim 16 wherein the tube position lock is provided by securing a tube within a strain relief collar cavity.

18. The manifold of claim 17 wherein the tube position lock is a set screw that exerts lateral force on a tube in the strain relief collar cavity.

19. The manifold of claim 10 wherein the clamp comprises a frame selectively secured to and offset from the bottom surface of the manifold body and a clamp pad cooperatively engaging the frame and positioned between the frame and the bottom surface of the manifold body forming a clamp cavity for receiving a microfluidic device wherein the distance between the clamp pad and the bottom surface of the manifold body is selectively adjustable to adjust the distance between a microfluidic device inserted in the clamp cavity and the bottom surface of the manifold body and to

adjust the force of the face seal formed between the elastomer layer of the microfluidic device and the sealing end faces of interconnect tubes extending from the bottom surface of the manifold body.

20. A degassing system for a microfluidic cavity element which comprises:

(a) a microfluidic cavity element characterized by a selected depth, width and height wherein at least a portion of a wall forming the cavity is a gas-permeable substantially liquid impermeable membrane, the membrane having an inner surface in contact with liquid in the cavity and an outer surface;

(b) a vacuum source in fluid communication with the outer surface of the membrane.

21. The degassing system of claim 20 wherein the vacuum source is provided to the outer surface of the membrane through a microfluidic channel.

22. The degassing system of claim 20 wherein the microfluidic device has an aspect ratio (width/depth) of 25 or greater.

23. The degassing system of claim 20 wherein the microfluidic device has an aspect ratio (width/depth) of 50 or greater.

24. The degassing system of claim 20 wherein at least a portion of two walls forming the channel are gas-permeable substantially liquid impermeable membranes.

25. The degassing system of claim 20 comprising two or more microfluidic channels in the same microfluidic device wherein in each channel at least a portion of a wall forming the channel is a gas-permeable substantially liquid impermeable membrane.

26. The degassing system of claim 20 wherein the membrane is formed from polydimethoxysiloxane.

27. The degassing system of claim 20 wherein the membrane is formed from polytetrafluoroethylene.

28. The degassing system of claim 20 wherein the membrane is formed from microporous or nanoporous solids.

29. The degassing system of claim 20 wherein the membrane is formed from hydrophobic microporous silicon.

30. A microfluidic device having the degassing system of claim 20.

31. The microfluidic device of claim 30 wherein the channel or channels to which vacuum is applied have aspect ratios (width/depth) greater than about 25.

32. The microfluidic device of claim 30 which is formed as a multiple layer laminate.

33. The microfluidic device of claim 32 which comprises a vacuum transfer layer and a vacuum distribution layer.

34. The microfluidic device of claim 30 wherein the membrane is formed from polydimethoxysiloxane.

35. The microfluidic device of claim 30 wherein the membrane is formed from polytetrafluoroethylene.

36. The microfluidic device of claim 30 wherein the membrane is formed from microporous or nanoporous solids.

37. The microfluidic device of claim 30 wherein the membrane is formed from hydrophobic nanoporous silicon.

38. The microfluidic device of claim 30 wherein the microfluidic cavity element is a sedimentation channel.

39. The microfluidic device of claim 38 wherein the microfluidic device is formed as a multiple layer laminate.

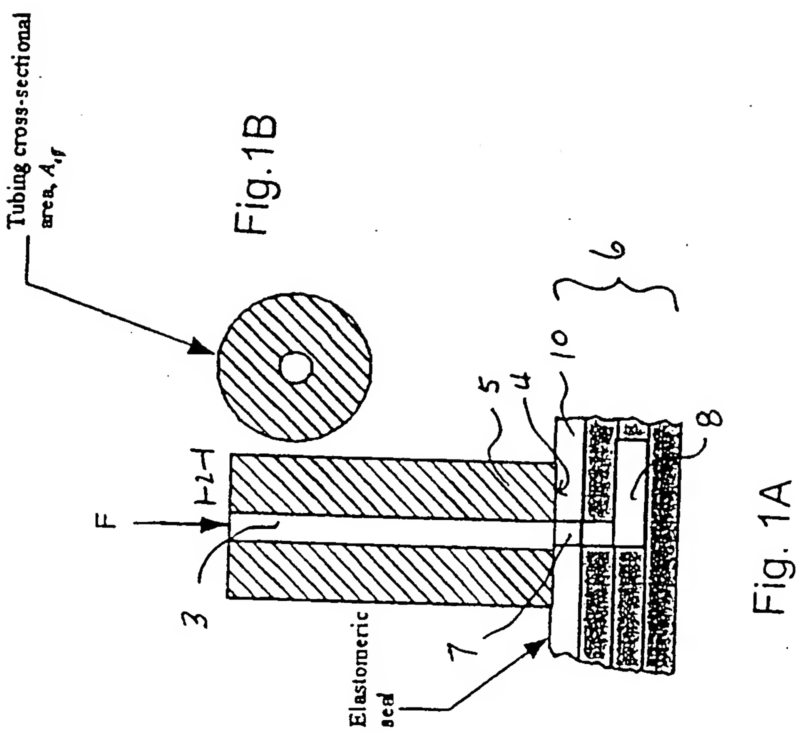

Tubing cross-sectional area, A_{tf}
F
1-2-1
3
5
4
10
6
8
7
Elastomeric seal

Fig.1B

Fig. 1A

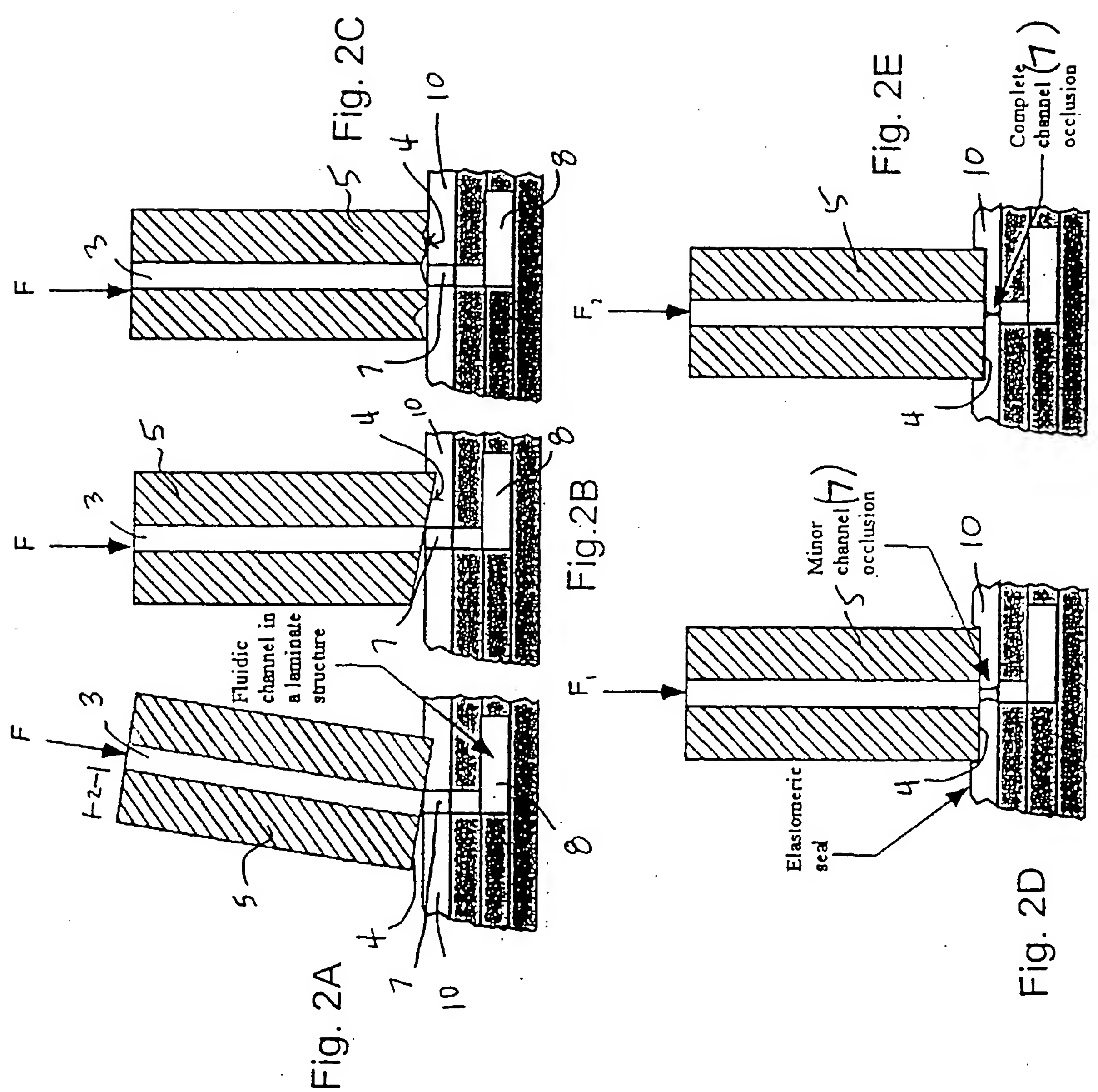


Fig. 2A

Fig.2B

Fig. 2C

Fig. 2D

Fig. 2E

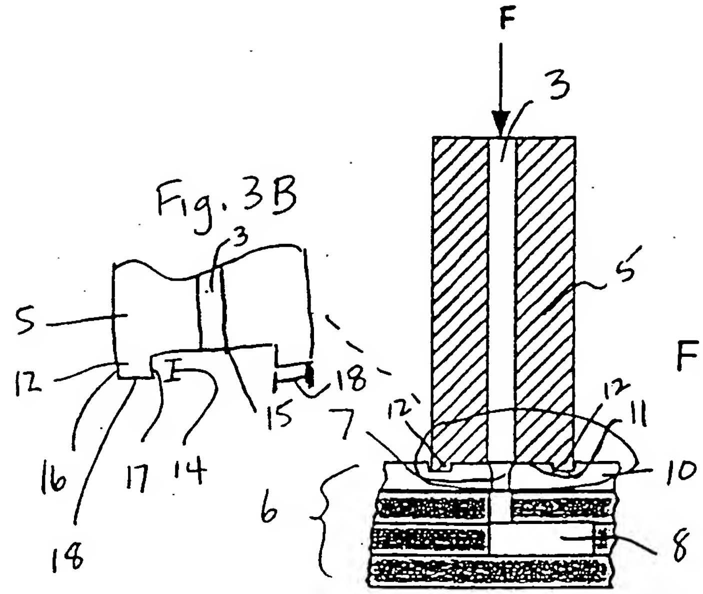

F
3
5
Fig. 3B
3
5
12
16
17
14
15
18
18
12'
12
11
7
10
6
8

Fig. 3A

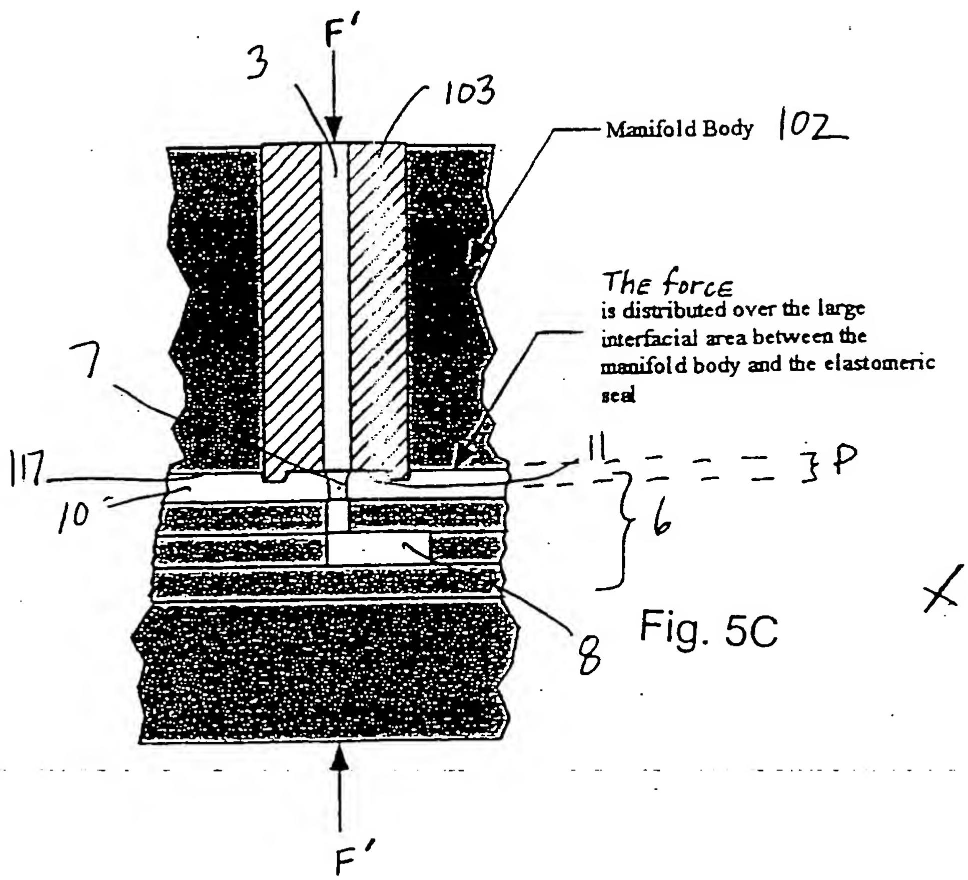

3
F'
103
Manifold Body 102
The force
is distributed over the large
interfacial area between the
manifold body and the elastomeric
seal
7
117
10
11
P
6
8
F'

Fig. 5C

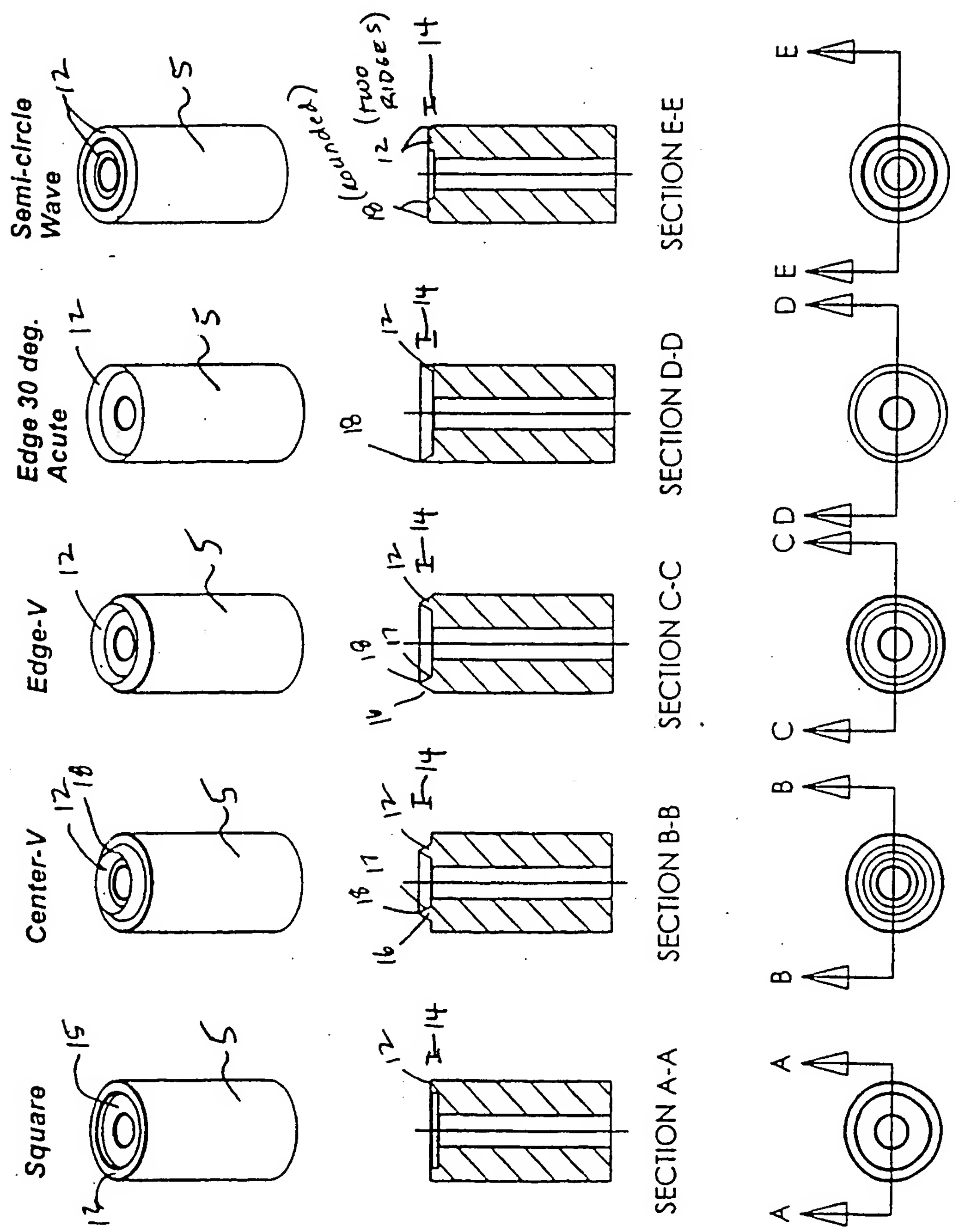


Fig. 4A

Fig. 4B

Fig. 4C

Fig. 4D

Fig. 4E

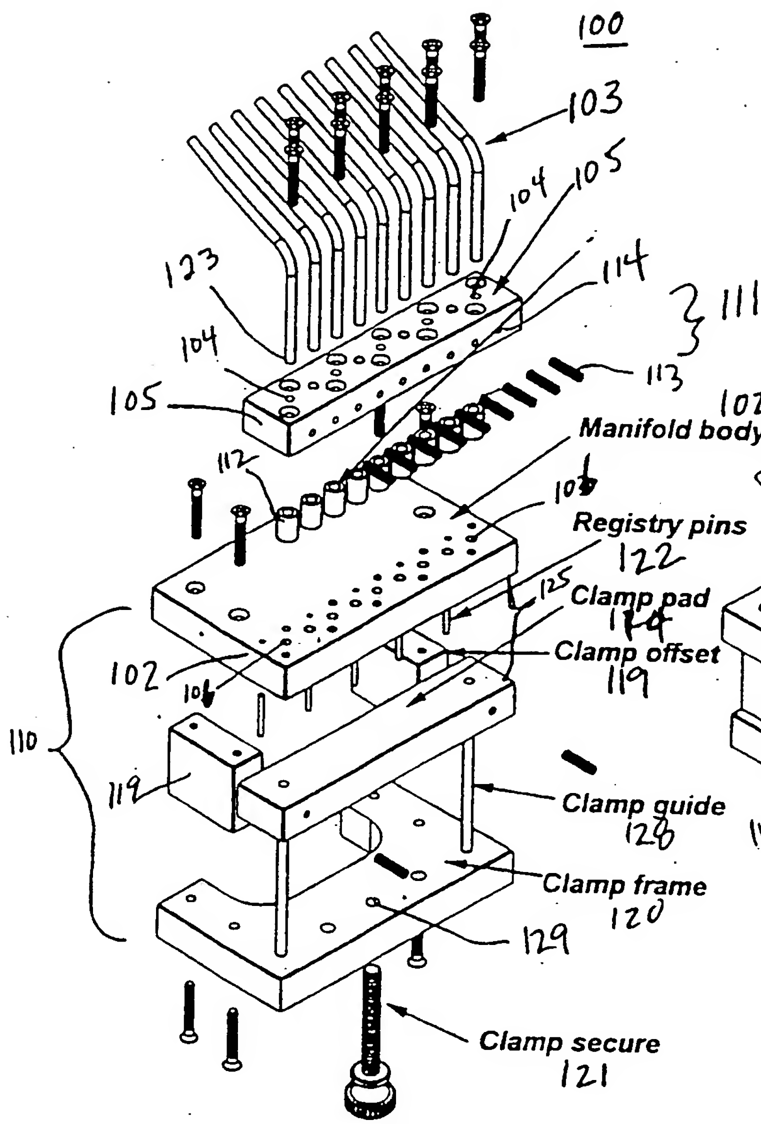

100
103
104
105
123
114
111
104
113
105
102
Manifold body
112
108
Registry pins
122
125
Clamp pad
124
Clamp offset
119
102
106
110
119
Clamp guide
128
Clamp frame
120
129
Clamp secure
121

Fig. 5B

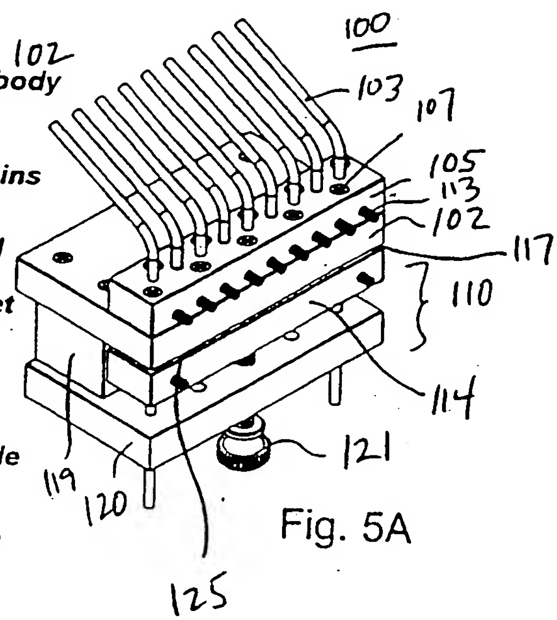

100
103
107
105
113
102
117
110
114
121
119
120
125

Fig. 5A

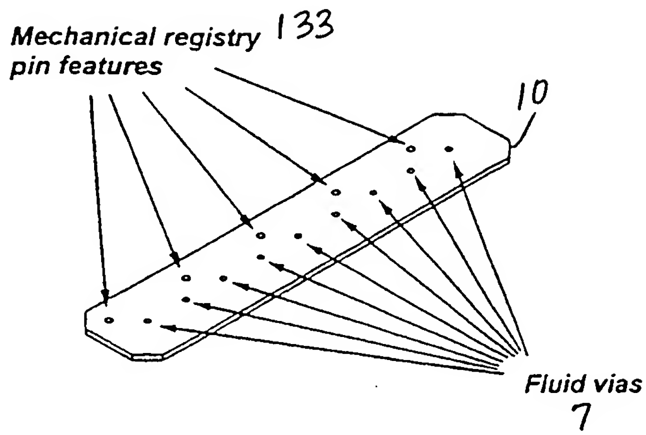

Mechanical registry pin features
133
10
Fluid vias
7

Fig. 6A

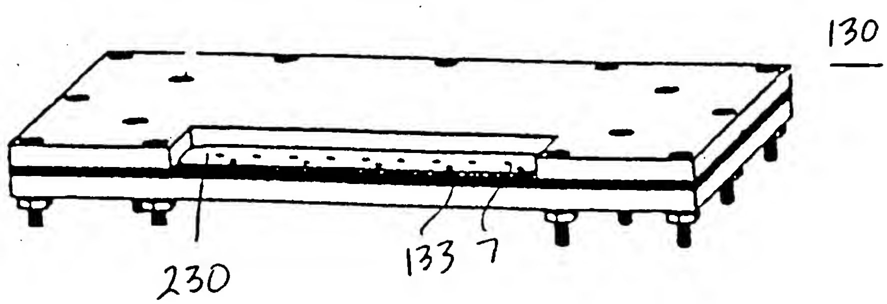

130
230
133
7

Fig. 6B

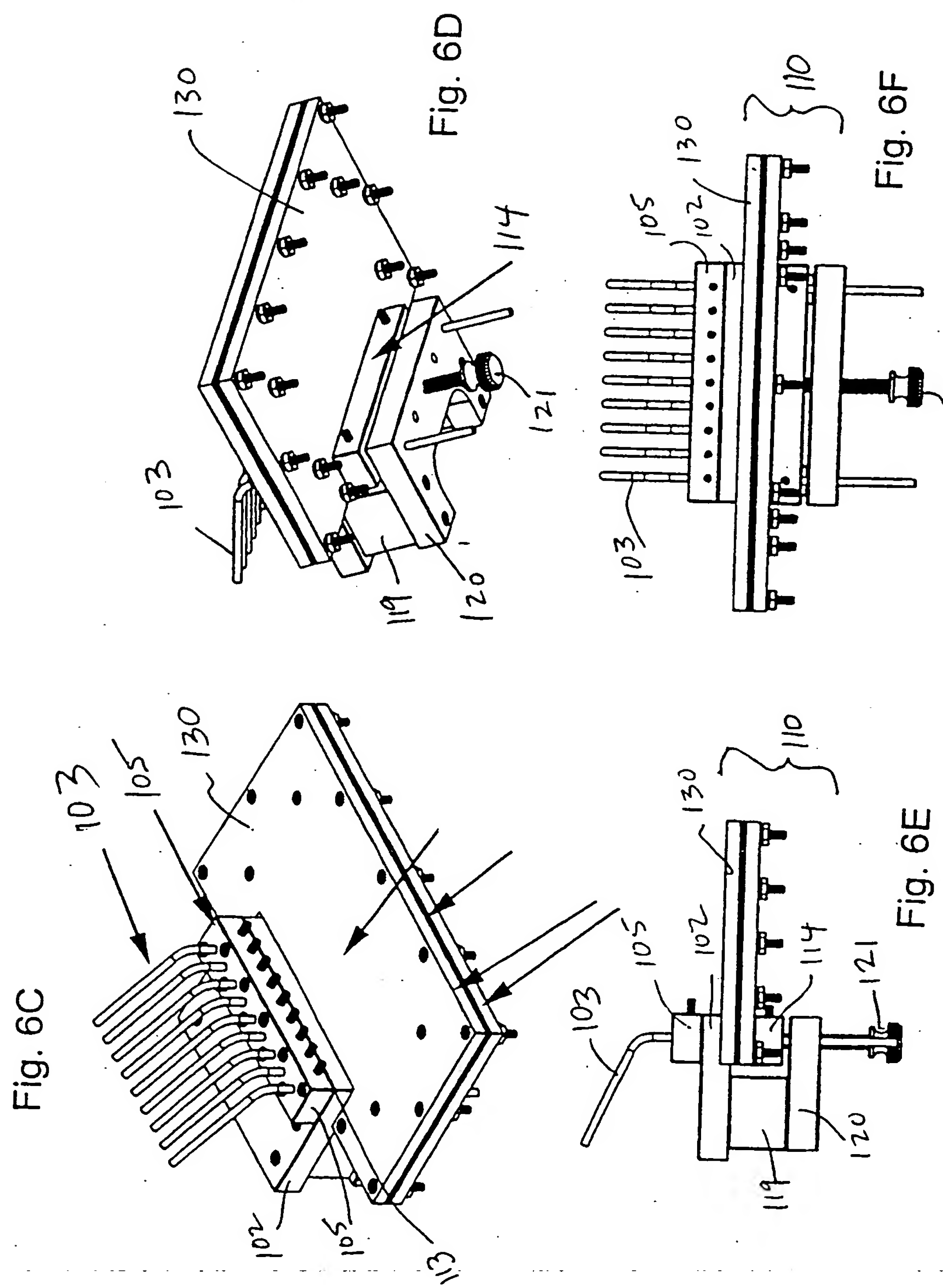
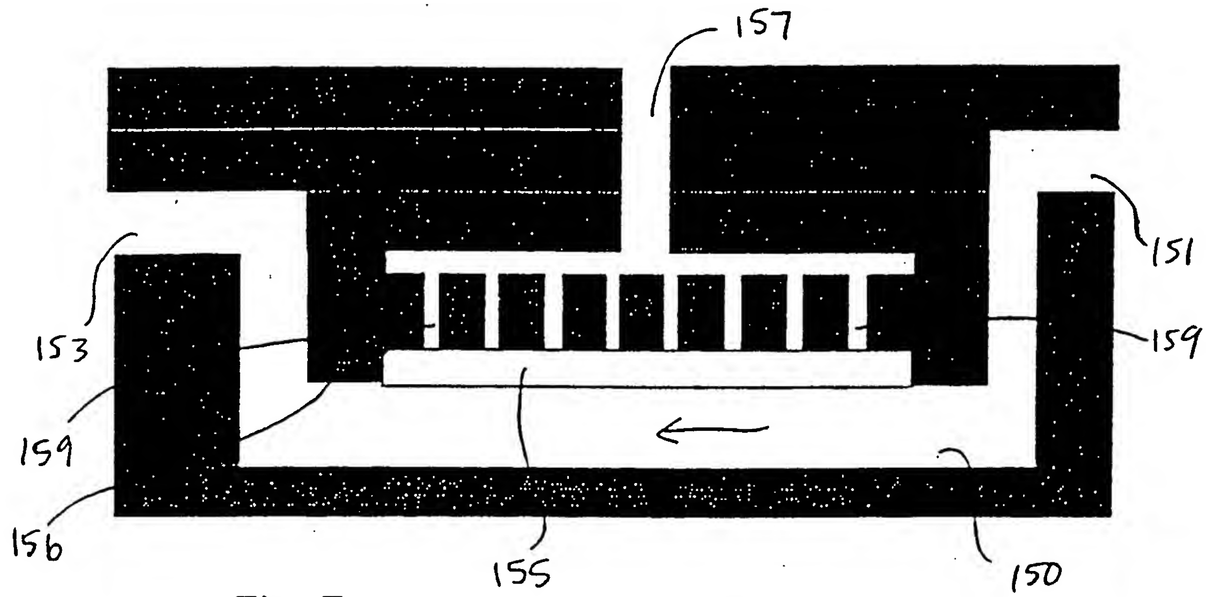


Fig. 6C

Fig. 6D

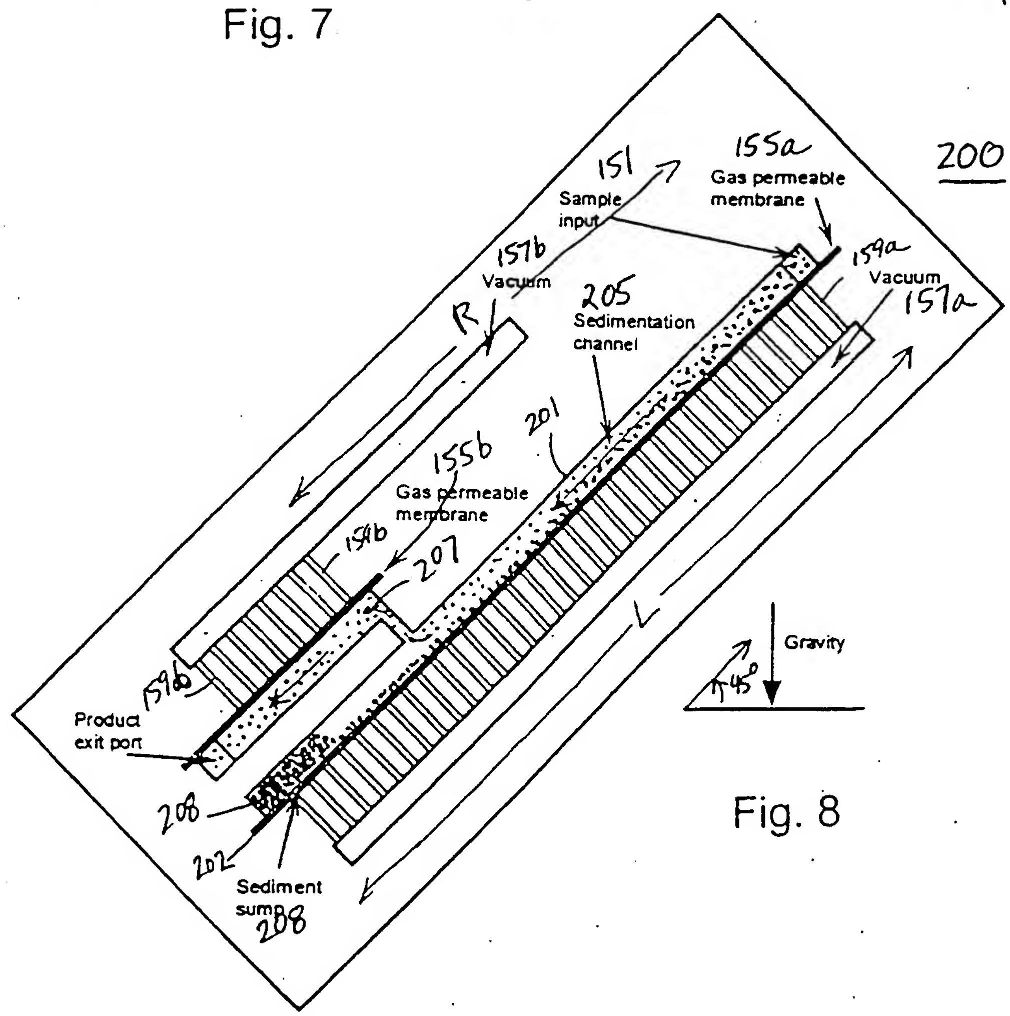
Fig. 6E

Fig. 6F



157
151
153
159
159
156
155
150

Fig. 7



200
151
Sample input
155a
Gas permeable membrane
159a
Vacuum
157a
157b
Vacuum
R
205
Sedimentation channel
201
155b
Gas permeable membrane
159b
207
159b
Product exit port
208
202
Sediment sump
208
L
Gravity
45°

Fig. 8

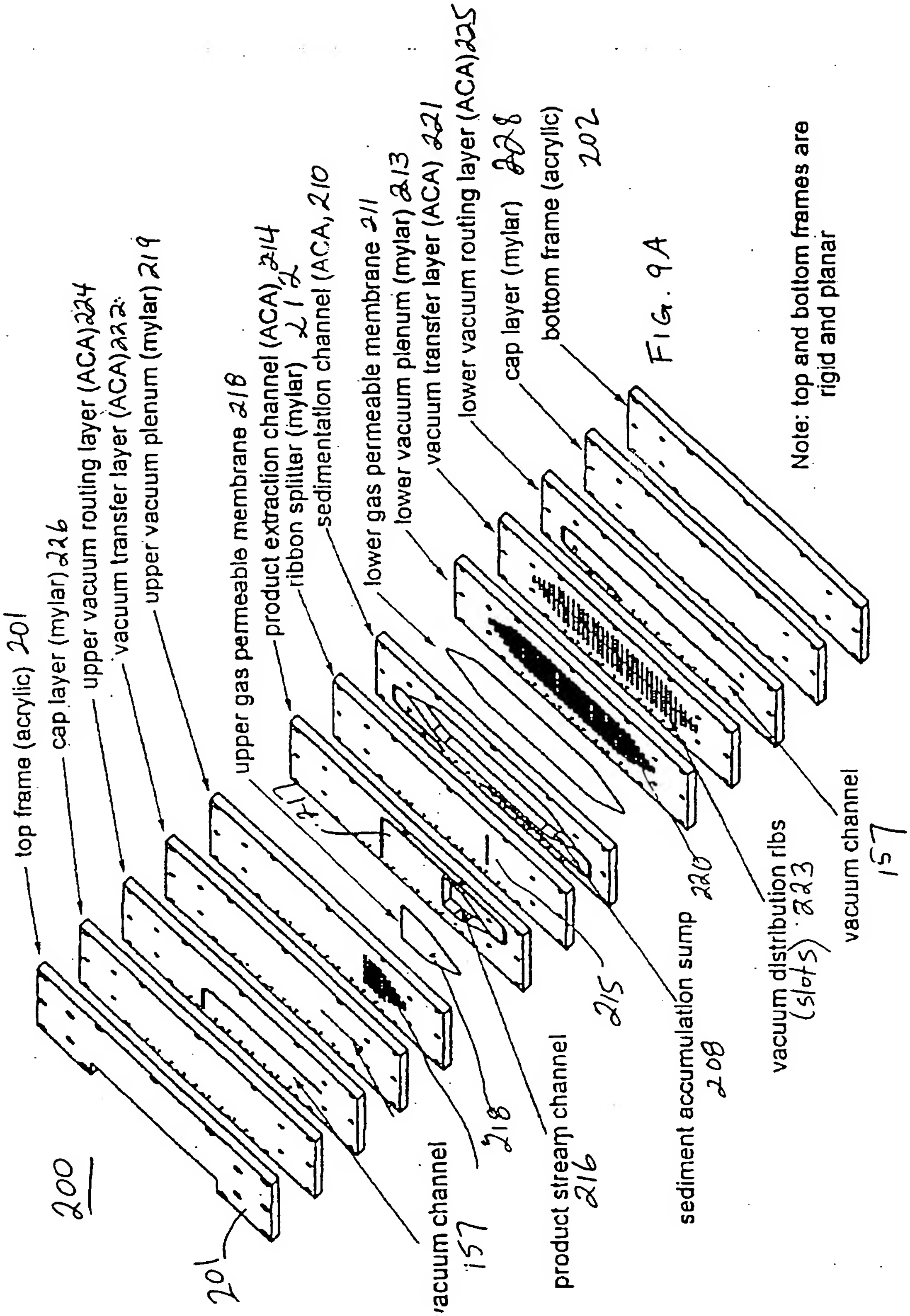

200
top frame (acrylic) 201
cap layer (mylar) 226
upper vacuum routing layer (ACA) 224
vacuum transfer layer (ACA) 222
upper vacuum plenum (mylar) 219
upper gas permeable membrane 218
product extraction channel (ACA) 214
ribbon splitter (mylar) 212
sedimentation channel (ACA, 210
lower gas permeable membrane 211
lower vacuum plenum (mylar) 213
vacuum transfer layer (ACA) 221
lower vacuum routing layer (ACA) 225
cap layer (mylar) 228
bottom frame (acrylic) 202
Note: top and bottom frames are rigid and planar
vacuum channel 157
vacuum distribution ribs (slots) 223
220
sediment accumulation sump 208
215
product stream channel 216
218
217
vacuum channel 157
201

FIG. 9A

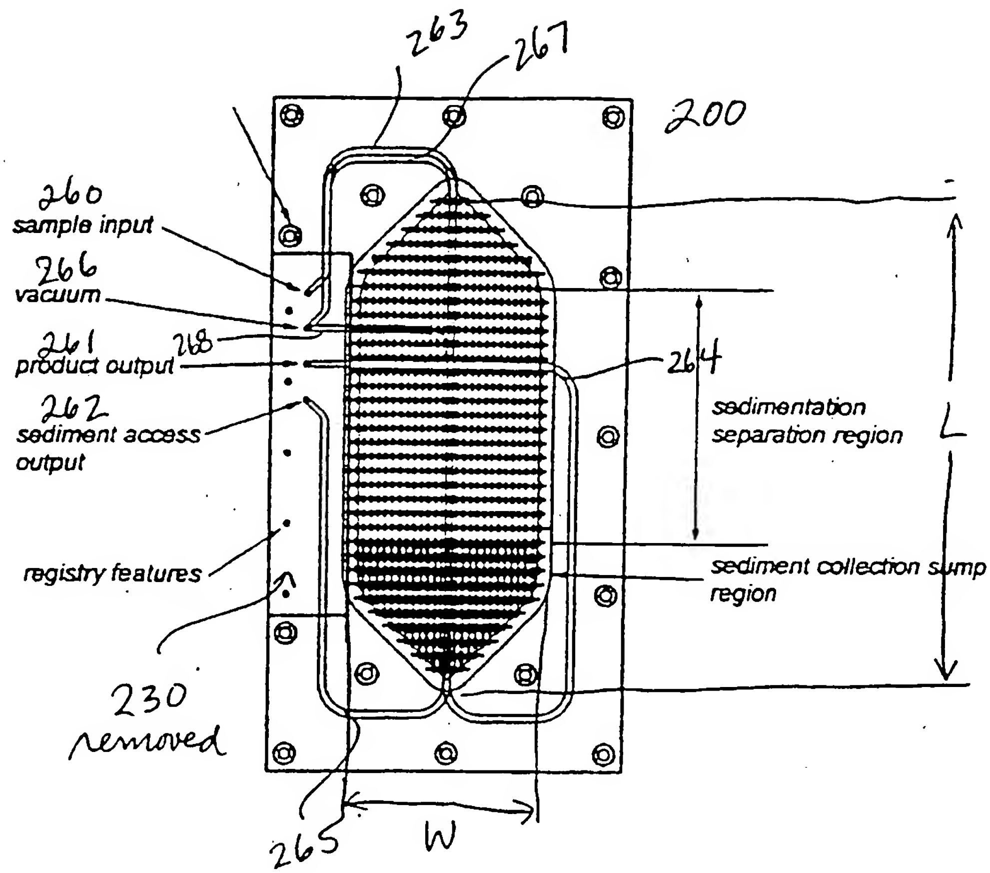

263
267
200
260
sample input
266
vacuum
261
268
product output
262
sediment access output
264
sedimentation separation region
L
registry features
sediment collection sump region
230
removed
265
W

Fig. 9B

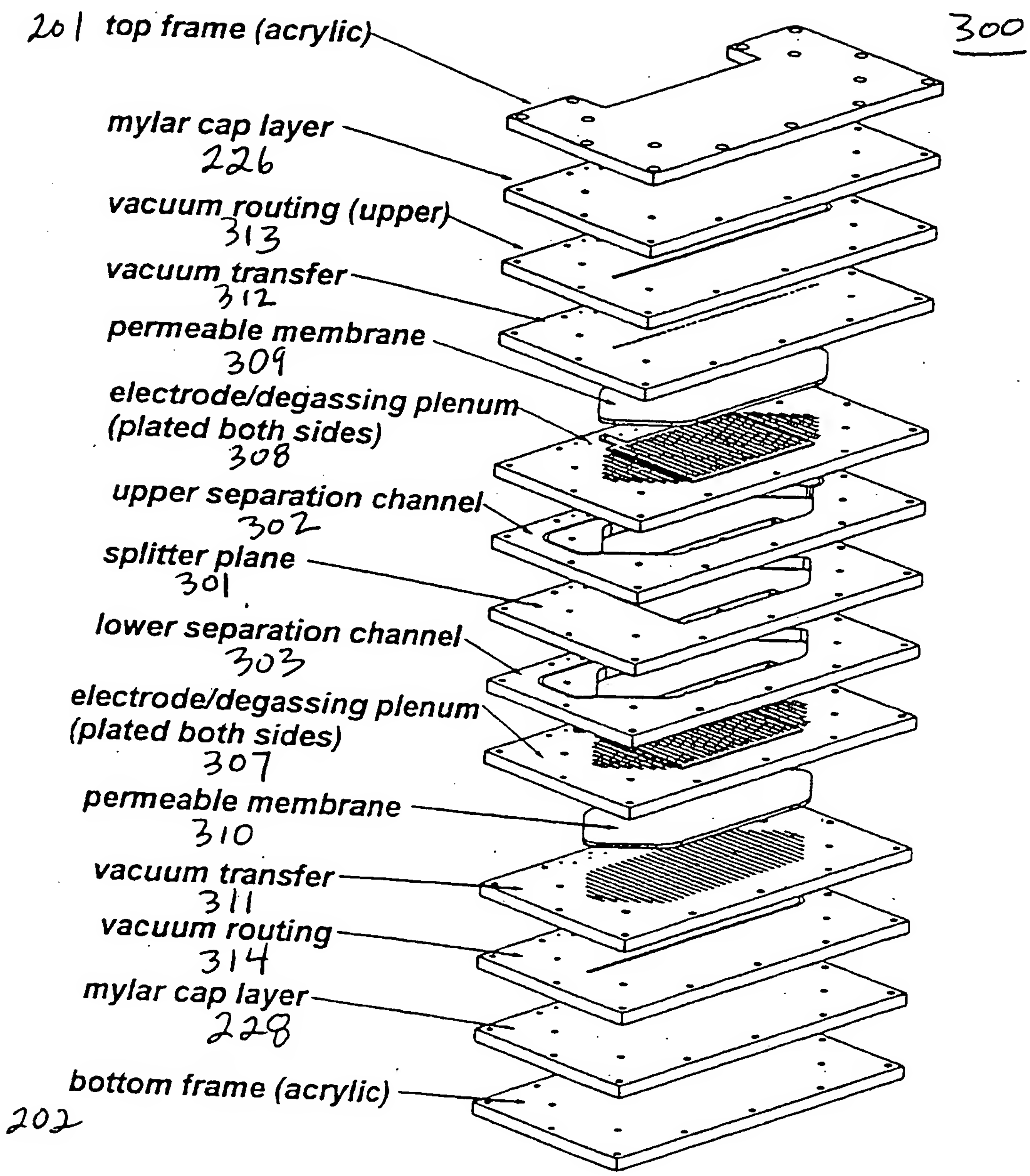

300
201 top frame (acrylic)
mylar cap layer
226
vacuum routing (upper)
313
vacuum transfer
312
permeable membrane
309
electrode/degassing plenum
(plated both sides)
308
upper separation channel
302
splitter plane
301
lower separation channel
303
electrode/degassing plenum
(plated both sides)
307
permeable membrane
310
vacuum transfer
311
vacuum routing
314
mylar cap layer
228
bottom frame (acrylic)
202

Fig. 10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/20698

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : G01N 27/26; F16L 35/00
US CL : 285/26,328,189,331; 422/100; 204/601; 95/46; 96/6
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 285/26,328,189,331,917

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EAST: microfluidic, class 285, class 95, class 96, class 204, class 422

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,053,060 A (KOPF-SILL et al) 01 October 1991 (01-10-91), entire document	1-39
A	Us 5,443,890 A (OHMAN) 22 August 1995 (08-22-95), entire document.	1-39
A	US 5,890,745 A (KOVACS) 06 April 1999 (06-04-99), entire document.	1-39
A,P	US 6,042,709 A (PARCE et al.) 28 March 2000 (28-03-00), entire document.	1-39
A,P	US 6,090,251 A (SUNDBERG et al.) 18 July 2000 (18-07-00), entire document	1-39

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
08 November 2000 (08.11.2000)

Date of mailing of the international search report
21 DEC 2000

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